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Excretion of Sex Hormones in Abnormalities of Puberty[1,2,3]

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THE INTERNAL SECRETIONS in childhood influence growth, metamorphosis and metabolic reactions. Growth rate and certain aspects of metabolism are easily studied. A different situation exists in regard to abnormalities of metamorphosis from childhood to adult life since they are not often recognized until the time when the normal changes should occur. Technics by which these processes may be more thoroughly studied have recently become available. Foremost among these is the determination of the sex hormones in the urine. In the last 6 years we have determined the levels of sex hormone excretion in children for evaluation as an index of future metamorphosis as well as for an index of abnormalities in development which had already become manifest. The information derived may thus be correlated with other data concerning these abnormalities.

There are very few data on sex hormone excretion in abnormalities of childhood. This is because normal standards had not been established through childhood and puberty, and it is only by means of the standard values determined in one's own laboratory that comparison of abnormal excretion rates can well be judged. The available material in this field has been summarized elsewhere (1).

METHODS

The methods of analyses for estrogens, 17-ketosteroids and pituitary gonadotropins have been reported (1) and only a brief summary is given here. Assays were made on complete 24-hour collections of urine.

Pituitary gonadotropic hormone. Pituitary gonadotropic hormone was precipitated from the urine with 95 per cent ethyl alcohol, using essentially the original technic of Aschheim and Zondek. Assay was performed on inbred, immature, female mice (Bar Harbor C_{57}) between 19 and 21 days of age and weighing between 6 and 8 gm. The urine was usually concentrated so as to permit detection of a minimum of 20 mouse units for the 24-hour specimen. One mouse unit (M.U.) is defined as the minimal amount of extract which, when injected in five aliquots over a period of 48 hours, will produce vaginal opening 96 hours after the first injection. Although the criterion of vaginal opening

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[1] The normal controls in this paper were established in collaboration with a Growth Study, funds for which were given to Harvard University by the Rockefeller Foundation.

[2] Reported at American College of Physicians and at the Association of American Physicians (*Trans. Ass. Am. Physicians* 55: 306, 1940). Additional data have been accumulated since then and are incorporated in this paper.

[3] This is reprint No. 573 of the Cancer Commission of Harvard University.

for determining gonadotropic activity is probably not as specific as others, such as follicle stimulation or an increase in ovarian or uterine weight, it is adequate to detect significant variations from the normal.

Estrogens and 17-ketosteroids. The urinary estrogens and 17-ketosteroids were extracted with benzol by the method of Smith and Smith (2). An aliquot of the benzol extract was then used for assay of the total estrogens. No attempt was made to separate the estrogens into their various components since the quantity of material available was much too small for such studies. The estrogens were assayed on inbred mice (Bar Harbor C_{57}) or rats (Slonaker strain) with a modification of the Allen-Doisy method. The 17-ketosteroids in the remaining extract were separated from the estrogens, using in principle the method of Gallagher, *et al.*, (3). Values are expressed in international unit equivalents of estrone.[4] The technic of assay was that described by Oesting (4) modified for the photoelectric colorimeter (5). Conditions such as temperature, light and purity of reagent were kept as uniform as possible. Values are expressed as milligrams equivalent of crystalline androsterone.[5]

In view of the rapid strides in the development of technics of assay and in the chemical identification of the various hormones, standard methods should be available so that the actual values obtained in each laboratory can be compared with each other. Unfortunately, however, normal values of different investigators differ and therefore cannot always be directly compared. Consequently, the individual laboratory must at present depend upon its own set of standard figures for comparison with those obtained in disease. This has been done in the group of cases presented here by adhering to the original technics as much as possible because a proportion of our data for both normal and abnormal cases has been accumulated over the past 6 years and hence before the advent of new information and possibly better methods of estimation.[6]

RESULTS

Normal controls. The data on 104 normal control children have been reported in detail elsewhere (1). There is a steady but slight increase in 17-ketosteroids and estrogen excretion in both sexes from the ages of 6 to 10 years. After this the excretion level of 17-ketosteroids rises more abruptly in boys, as does the estrogen excretion in girls. However, there is also a consistently increasing level of excretion of 17-ketosteroids in girls and of estrogens in boys. Approximately 1.5 years before the menarche, a cycle of estrogen excretion which gradually increases in amount develops in girls. During this period and thereafter it is necessary to determine the estrogen excretion repeatedly. This has not been possible in some of the abnormal girls in our present series, so that the excretion levels can only be compared with minimal or maximal rates. No cycle of 17-ketosteroid excretion was found in either sex nor any cycle of estrogen excretion in boys. Variations in the 17-ketosteroid excretion occur from day to day, but these are seldom greater and usually less then 25 per cent of the mean of a series of consecutive daily assays. Consequently, several determinations on carefully collected urine specimens are usually adequate. The same may be said for estrogen assays in the male.

Tests for the presence of pituitary gonadotropic hormone in the urine with the technic described are usually negative in normal girls before the age of 11 and in normal boys before the age of 13. Such a negative response does not imply that gonadotropic function is lacking before these ages. The steady increase in the excretion levels of the estrogens and of the 17-ketosteroids in the younger age groups suggests such an activity. Therefore a negative response merely means that the method is inadequate to detect very small amounts of the hormone in the urine, even though it may be present. A positive response prior to these ages and elevated levels thereafter may be considered as

[4] The crystalline estrone (Theelin) was supplied for standardization through the courtesy of Dr. E. A. Sharp of Parke, Davis & Co., Detroit, Mich.

[5] The crystalline androsterone which was used as a reference standard was generously supplied by Dr. Erwin Schwenk of the Schering Corp., Bloomfield, N. J., and by Dr. Ernst Oppenheimer of the Ciba Pharmaceutical Products, Inc., Summit, N. J.

[6] In the past two years parallel assays of the urinary 17-ketosteroids were carried out using several accepted technics described in reference 5. Although the titers of the same specimen varied with the different methods, the trends in excretion rates were identical.

indicative of unusual pituitary activity or of limited gonadal response. Assays for the pituitary gonadotropins were not made in every case.

Abnormal Cases

In the term abnormal puberty is included all degrees of variation from average growth and development, although many of these children may eventually become normal adults. On the basis of the standards derived from the previous study (1) an impression can be formed of the relative levels of excretion of the sex hormones in children whose development is atypical. The rates of excretion in both normal and abnormal children of the same chronologic age have been arranged in tables.

The children included in this study, so far as we know, have only functional endocrinopathies. Observations on children with functioning tumors have been reported elsewhere (6). Functioning tumors of endocrine origin give rise to striking increases in the rate of sex hormone excretion while in the cases described here the variations from the normal range are not so dramatic. This indicates that marked increases in hormone excretion may be due to hyperfunctioning tumors, while slight to moderate increases are more suggestive of functional abnormalities or of benign hyperplasias of the endocrine organs. One example of this was in a 2-year-old child with a hyperfunctional abnormality of the pituitary gland with true pubertas praecox, which was shown at autopsy to be due to stimulation from a nonmalignant tumor arising in the hypothalamus. The hormone excretion levels were similar to those of a normal young adult and not the very high levels found in true hyperfunctioning tumors.

Precocious puberty. This is a manifestation of an early stimulus to normal sexual growth and development representing an abnormally early adolescence. This is frequently but not necessarily accompanied by precocious somatic development as well. There were 8 children in this group (table 1), all but two of whom were very advanced in sexual development. *Cases 2* and *8* were apparently normal children, 11 years old, but who were slightly advanced in development. This observation was in accord with the sex hormone excretion rates which were in the normal range for children about 13 years of age. These children therefore appeared to represent a physiological variation of normal puberty which is more a matter of time of onset than of form. The other 6 children represent cases of far greater abnormalities for they demonstrated sex and somatic changes at very early ages. Gonadotropic assays were performed for 6 of these 8 children and 5 had elevated excretion levels on one or more occcasions. At these ages such findings are usually indicative of pituitary overactivity and are comparable to the values for normal children at or near puberty. In 7 of the cases there was an elevation of the excretion level of both estrogens and 17-ketosteroids. In *case 7* there was an elevation of urinary estrogen only. She was a tall girl who was menstruating and had developed secondary sex characteristics. The estrogen excretion levels in this person differed little from those of *case 6*, but the latter also had an elevated 17-ketosteroid excretion, and, interestingly enough, had not menstruated.

Retarded puberty and growth. In the 14 cases of retarded puberty the reduced level of the estrogen and 17-ketosteroid excretion parallels the degree of physical retardation (table 2). For example, *case 19*, was a girl, 14 years old, who was considerably retarded in sexual metamorphosis. The excretion level of the 17-ketosteroids was normal, but there was a definite reduction in estrogen excretion. By contrast, *case 16* was very retarded, both physically and sexually. The excretion values for both estrogens and 17-ketosteroids were approximately those of an 8-year-old- girl. Ten months after the first assays there was an elevated titer of pituitary gonadotropin. In *case 22* growth was very slow and the signs indicative of puberty had not appeared. The excretion level of estrogens was not unusually low, but the 17-ketosteroid values were subnormal when she was first studied. Two years later, at the age of 17, this girl still had not arrived at the menarche, but there was a rapid development of the secondary sex characteristics and an increase of 3 inches in height. It is to be noted that at this later time the 17-ketosteroid and the gonadotropin excretions were normal for a girl at puberty. *Case 16* (see above) differed from *case 22* primarily in the

TABLE 1. HORMONE EXCRETION STUDIES IN 8 CASES OF PRECOCIOUS DEVELOPMENT

Pt.	Age, yr., mo.	Bone Age, yr.	Wt., lb.	Ht., in.	Estrogens I.U. 24 hr.	17-Ks mg./24 hr.	Gonadotropin M.U./24 hr.	Clinical Remarks	Normal Values for Chronological Age: Estrogen I.U.	Normal Values for Chronological Age: 17-Ks mg.	Normal Values for Chronological Age: Gonadotropin M.U.
Male patients											
1[1]	4—3	7.5	61.5	43.0	43.0	3.5	>120	Muscles large; genitals, testes, prostate enlarged. At age 5–6 bone age 11–3; ht. 47.5 in.; wt. 60 lb.; genitals further advanced, voice low; normal sugar tol., blood cholesterol 101 mg. %	6.0 (4–9)	3.2 (2.4–4.8)	<20
2[1]	11—1	13.5	90.0		84.0 40.0	17.4 14.4	>120 <80	Slightly advanced development	30.0 (10–60)	11.0 (8.5–13.0)	<20
Female patients											
3[2]	4—0	7	46.5	42.0	296.0 130.0	8.6 9.2	>40 >36	Continued development; breasts and uterus enlarged; no menses	8.0 (5–10)	2.5 (1.5–3.6)	<20
4[3,4]	4—1 4—4	8	64.0	49.8	160.0 96.0	4.0 5.4	ND <40	Breasts enlarged. Progressive development; B.M.R.+19%			
5[2]	5—5	10	42.0	48.5	154.0 89.0 32.0 28.0	6.5 5.5 7.5 7.7	>87 <22 <37 <26	Progressive development; pubic hair developed 6–6. Breasts enlarged; vaginal bleeding at 6–8, wt. 47.3, ht. 50.3. B.M.R.—5%	8.0 (5–10)	3.0 (1.8–3.6)	<20
	6—0 6—8				48.0 45.0	7.2 6.8	>60 <20		9.0 (5–15)	3.0 (2.0–4.2)	<20
6[3,4]	7—1	12	75.2	53.0	176.0 80.0 112.0 64.0 130.0	11.1 10.6 12.1 9.0 8.4	ND <30 <30 ND <30	Moderately progressive development. Breasts enlarged	20.0 (5–35)	4.2 (3.0–6.0)	<20
	7—5 8—2				96.0 84.0	10.4 14.9	<36 <30		20.0 (10–35)	4.9 (3.6–7.5)	<20
7[3,4]	7—1 7—1 7—2 7—6	7	68.0	55.0	136.0 112.0 168.0 119.0	6.0 5.9 6.3 5.0	>28 <28 <28 >18	Progressive development; breasts enlarged, vaginal bleeding. Blood cholesterol 154 mg.%, B.M.R.—19%			
8[3]	11—2	14–15	131.2		150.0 125.0 125.0	12.0 8.4 9.7 10.8 9.2	ND	Short and stocky, slightly advanced adolescence with menses at 10–11. Blood sugar, 70 mg.%. Blood cholesterol 84 mg. %	76.0 (25–150)	9.6 (6.0–10.8)	±20

[1] Hair on upper lip in addition to pubic hair. [2] Body configuration feminine, advanced for age. [3] Also axillary hair.
[4] Vaginal epithelium cornified. [5] Average of five determinations.
ND—not determined. Pubic hair was present in every case. Figures in parentheses represent range of normal values per 24 hours.

relatively low estrogen excretion. The advent of pubertal changes in *case 16* was signified by the excretion rate of gonadotropic hormone as evidenced by the subsequent sexual development with the onset of menstruation two years later. This is analogous to observations reported by us (1) in normal children at an earlier age in whom the first excretion of detectable amounts of gonadotropic hormone generally accompanied the onset of striking pubertal metamorphosis.

The care to be exercised in the interpretation of findings during the period of puberty is demonstrated by *case 20*, a girl, who was 14 years and 8 months of age at the time of study and who showed no development of secondary sex characteristics. The urine of this girl was collected twice a week over a period of 4 weeks. If only the first 5 samples had been assayed for estrogens the cyclic excretion of these would have been overlooked. However, the last determinations in this series showed that there was a cyclical output of estrogens. The excretion rate of the 17-ketosteroids was at the lowest limits of normal. Three months later breast development began and the first of subsequently normal menstrual cycles appeared just a year later. She grew 3.5 inches during this year. This, therefore, was a girl with a completely neutral prepubertal configuration in whom prognosis of a normal development could be made because of the cyclical nature of estrogen excretion. The sex hormone excretion of this child of 14 years and 8 months corresponded with the usual estrogen excretion cycles of normal 11 or 12-year-old girls and the subsequent course was similar to that found in more normal female subjects

In the males with retarded puberty and growth there were similar findings. Thus *case 11*, who was growing slowly but who otherwise was normal, had hormone excretion values that

TABLE 2. HORMONE EXCRETION STUDIES IN 14 CASES OF RETARDED GROWTH AND SEXUAL DEVELOPMENT

Pt.	Age, yr., mo.	Bone Age, yr.	Wt., lb.	Ht., in.	Estrogens I.U./24 hr.	17-Ks mg./24 hr.	Gonadotropin M.U./24 hr.	Clinical Remarks	Normal Values for Chronological Age: Estrogens I.U.	Normal Values for Chronological Age: 17-Ks. mg.	Normal Values for Chronological Age: Gonadotropin M.U.
					Male patients						
9	12 — 1 12 — 1 12 — 2 13 — 2[2] 14 — 1	6	51.2	45.7	54 30 42 48 18	3.9 5.4 4.5 5.6 5.6	<40 <40 ND >66 ND	Short and stocky; genitalia infantile. No body hair. Very slow development, even on intensive hormonal therapy; B.M.R.—19%	30.0 (10–60)	13.0 (9.0–15.0)	±20
10	12 — 8[3] 13 — 3[4]	12	84.0	58.5	22 19	5.1 6.0	<20 <20	Early masculine configuration, slight pubic hair. Beginning to grow but small for age, B.M.R.+6%	40.0 (20–80)	15.0 (10.0–19.0)	± 20
11	14 — 4	13	81.5	61.5	28	9.4	<40	Normal configuration, genitalia slightly retarded and sl. pubic hair; B.M.R. −11%			
12	14 — 6 14 — 9 14 — 10 15 — 6	13	78.7	60	10 15 72 57	4.0 4.9 9.0 9.1	<20 <26 ND >100	Neuter configuration, genitalia infantile no pubic hair; B.M.R.± 0%			
13	15— 4	11–12	80.0	58.9	30	6.8	ND	Neuter configuration, genitalia infantile no pubic hair; B.M.R.+14%			
14	15 — 5 16 — 9 17 — 4 18 — 9[5] 18 — 11 19 — 4	10	63.0	54.5	260 320 192 184 50 280	ND 2.7 3.6 4.5 6.0 6.8	<40 ND ND >21 >45 >20	Neuter configuration, genitalia infantile no pubic hair; B.M.R.+4%			
15	18— 3 19— 1	14	94.7	52.4	35 28	7.5 9.3	>80 >48	Short and fat, genitalia infantile. No body hair; B.M.R.−2%			
					Female patients						
16	12 — 1 12 — 10	Slightly retarded	61.5	51	32 20	6.8 6.0	<80 >108	No pubic hair, no breast development until 13 yr. 5 mo. First menses at 14 yr. 1 mo. B.M.R.+19%	240.0 (30–400)	9.6 (6.0–13.0)	±20
17	12 — 9 13 — 1	Slightly retarded	61.5	49.7	14 15	5.2 4.8	<20 <20	Neuter configuration, body hair very sparse, genitalia infantile, no breast development; B.M.R.+37%[1]. Grew after testosterone therapy.			
18	13 — 1 13 — 1 13 — 9	Normal	51.0	49.1	6 8 8	3.7 4.1 3.6	<20 <20 <20	Neuter configuration, body hair sparse, genitalia infantile; no breast development. Very sl. improvement with growth hormone; B.M.R.+8%	300.0 (40–500)	9.6 (6.0–13.0)	±20
19	14 — 0	slightly retarded	82.2	56.6	56	8.6	ND	Feminine configuration; sl. pubic hair, genitalia retarded, breasts very small. Progressive improvement at 14 yr. 7 mo. with development of labia and breasts and increased hair; B.M.R.−4%	380.0 (50–600)	11.4 (9.0–15.0)	>20
20	14 — 7 15 — 0 15 — 6	Slightly retarded	80.0	55.7	10 20 24 30 24 270 432 144 30 450	8.0 7.2 8.4 7.6 8.7 8.1 7.8 8.4 7.2 9.0	ND	Neuter configuration, body hair sparse, genitalia infantile, no breast development. Marked improvement; development of secondary sex characteristics and first menses at 15 yr. 8 months. B.M.R.+20%			
21	15 — 1 15 — 3	Slightly retarded	63.0	52	30 14	6.2 4.5	<20 <15	Early feminine configuration, no body hair, genitalia infantile, slight development of right breast. B.M.R.—9%			
22	15 — 0 17 — 0	Retarded	79.5	59	75 80	4.0 15.0	<30 >60	Early feminine configuration, no body hair; genitalia infantile, no breast development. Breasts enlarged at 16 with progressive development thereafter, no menses at 17, B.M.R.−4%			

[1] Receiving thyroid. [2] On APL therapy. [3] Average 8 determinations. [4] Average 5 determinations. [5] On testosterone therapy.
ND—Not determined. Blood sugar in each case within normal limits.

were normal in ratio and only slightly low in amount. *Case 13* was very much retarded both sexually and physically and the excretion levels were very low for both estrogens and 17-ketosteroids. On the contrary, the last two determinations in *case 12* showed a sudden rise in pituitary gonadotropins, estrogens and 17-ketosteroids. This change occurred during the summer when he also developed sexually to a considerable extent. We considered this as the beginning of puberty and advised against therapy; he was sent away to school, and reports indicated

TABLE 3. HORMONE EXCRETION STUDIES IN 9 CASES OF ADIPOSO-GENITAL DYSTROPHY

Pt.	Age, yr., mo.	Wt., lb.	Ht., in.	Estrogens I.U./24 hr.	17-Ks mg./24 hr.	Gonadotropin M.U./24 hr.	Clinical Remarks	Normal Values for Chronological Age: Av. Est. & Range I.U.	Normal Values for Chronological Age: Av. 17-Ks & Range mg.	Normal Values for Chronological Age: Gonadotropin M.U.
							Male Patients			
23[1]	10 – 4	130.5	60.5	28.0	7.2	<60	Improved with thyroid and dietary therapy; B.M.R.—24%	22.0 (10–15)	9.4 (7.5–13.0)	<20
24	11 – 0	159	59.5	24.0 16.0	4.5 5.2	<20 <20	Had treatment for undescended testicles 2 mo. before observation. B.M.R.+34% (?)	30.0 (10–60)	11.0 (8.5–13.0)	<20
25	11 – 2	160	58.2	18.0	5.1	<80	Blood cholesterol 148 mg.%; normal sugar tolerance; improved with thyroid and dietary therapy; B.M.R.—9%			
26[2]	11 – 4 12 – 2 12 – 4 12 – 11 13 – 3	130.2	59.2	24.0 18.0 36.0 15.0 72.0	7.2 5.6 5.2 6.5 10.9	<80 ND ND <40 >34	Flat sugar tolerance curve; slight improvement with thyroid and dietary therapy; marked improvement with pregnant mare's serum; B.M.R.—22%	30.0 (10–60)	13.0 (9.0–15.0)	±20
27	11 – 5 13 – 6	83.5	51.0	40.0 45.0	7.0 8.4	ND <40	Blood sugar, 95 mg.%; improved with thyroid and dietary therapy; rapid metamorphosis at 15 yr. 3 mo.; B.M.R.—17%			
28	13 – 8	175	61.5	16.0 29.0	11.6 11.0	<20 <26	Normal sugar tolerance curve; marked improvement on regimen of thyroid, diet and pregnant mare's serum; B.M.R.—20%	40.0 (20–80)	15.0 (10.0–19.0)	±20
29	15 – 2 15 – 8	108.2	56.4	90.0 128.0	10.9 16.0	<20 <50	Seen first at age 7; some improvement with diet and thyroid, but still abnormal at present; B.M.R. —17%			
30[3]	16 – 0	179	66.1	75.0 105.0	7.5 7.5	<20 <20	Had treatment for undescended testicles 2 months before observation; B.M.R.—15%			
							Female Patients			
31	14 – 9	151	66.0	45.0	8.4	ND	Improved with diet and thyroid, but was beginning to show metamorphosis when first seen. B.M.R.—12%	380.0 (50–600)	11.4 (9.0–15.0)	>20

[1] Bone age advanced.

[2] Thyroid extract continued throughout. Pregnancy urine extract, 7700 U. for 4.5 months between first and second determination. Pregnant mare's serum, 4500 U. for 6 weeks between fourth and fifth determination.

[3] Bone age, 14 yr.

Roentgen of sella turcica normal in all cases; bone age normal except as indicated; body hair absent or sparse in all cases except *31*. The genitalia were infantile in all cases.

no growth in the subsequent 4 months. However when he returned home after 8 months he had developed sexually, had grown 3 inches in height and had gained 13 pounds in weight. It is, therefore, clear that this sudden rise in hormone excretion levels not only paralleled a physical change but also presaged a continued development.

The boys in this group who had the most marked growth retardation showed the most profound abnormality in the rate of sex hormone excretion. This was particularly true of *case 14*, age 19, who remains dwarfed and infantile although he has received endocrine treatment for the last 11 years including almost every type of pituitary growth and gonadotropic preparation which has been made available. In this patient the excretion of estrogens was

very high and of 17-ketosteroids very low, the latter at levels about normal for 4 years of age. In spite of the high estrogen excretion rate the body configuration was neuter. The testicles were like those of a completely immature child. Testosterone therapy which was commenced at 18 years and 9 months of age produced a striking change for about 6 months. The urinary estrogens decreased, the 17-ketosteroids increased, and, for the first time, the urine gave evidence of pituitary gonadotropic activity. Clinically, he seemed to be advancing not only sexually but with a definite increase in bone age. With the cessation of improvement, the urinary estrogen levels rose again, although the gonadotropic and 17-ketosteroid excretion remained unaltered. We are unable to explain the elevated estrogen levels, which are unusual in our experience for this type of case.

Adiposo-genital dystrophy is a frequent deviation from normal puberty. It is associated with marked obesity of the torso, infantile genitalia and gonads which are often undescended in the male. These characteristics often disappear spontaneously leading to a normal pubertal metamorphosis. It is to be distinguished from the obesity found in many vigorous children with rapid growth and sexual development and from the rare Frölich's syndrome which is characterized by delayed osseous development and growth, a flat blood-sugar curve, a somewhat low basal metabolism and a tumor of the pituitary gland. Determination of sex hormone excretion levels in cases of adiposo-genital dystrophy usually shows either low normal or moderately lowered 17-ketosteroid excretion with a normal or slightly elevated estrogen excretion. This additional evidence for the identity of this syndrome may explain the feminine configuration and delayed sexual development encountered in the disease.

Case 26, age 11 years, 4 months, when first seen was clinically typical of marked adiposogenital dystrophy with one undescended testicle which, on good authority retracted after an attack of chicken pox at 6 years of age. For 4.5 months between the first and second urinary determinations this patient was given gonadotropic therapy,[7] without any obvious effects. He was then given pregnant mare's serum,[8] for 6 weeks between the fourth and fifth urinary determinations. During these 6 weeks the physical development of the boy was remarkable. The descended testicle doubled in size, and the undescended testicle, although not large, could be felt high up in the scrotum. Hair developed over the mons, the body configuration became more masculine and he grew 1.7 inches, gaining only 2 pounds in weight. This great change in the physical configuration was accompanied by an increased excretion rate of 17-ketosteroids. The excretion level of gonadotropins became elevated, but this was to be expected since the determination was made while the boy was receiving pregnant mare's serum.

DISCUSSION

The value of studying the urinary excretion of the gonadotropic and sex hormones in endocrine abnormalities is clear since they may be of considerable aid in the diagnosis of the etiology and course, as well as in the prognosis of the response to treatment. Evidence exists that the urinary 17-ketosteroids and estrogens represent excretory products of steroids produced both by the gonads and the adrenal glands (7, 8, 9). This information is of considerable value in the interpretation of the data on the excretion of these hormones. It should be emphasized that in some of the cases reported here the deviation from the normal range is so slight that the excretion levels may possibly be considered normal. This pertains, primarily, to those patients who clinically were considered as cases representing borderline variations of normal puberty. In contrast the hormone excretion levels in the grossly abnormal patients are sufficiently out of the average range to warrant the supposition that they are definitely atypical. Similar trends of hormone excretion levels are found in analogous clinical abnormalities. The interpretations, therefore, are based largely on the accumulated data rather than on the individual case.

Precocious puberty. In general, in precocious puberty not caused by neoplasms, there is a moderate elevation in the urinary excretion of the gonadotropins, estrogens and 17-ketosteroids which approach levels characteristic for

[7] Pregnancy urine extract (Antuitrin S) 7700 units, Parke Davis & Co.

[8] Anterior-pituitary-like hormone (Anteron) 4500 units, Schering Corp.

adults. These levels are essentially the same as those for older children, with whom the degree of skeletal, somatic and sexual metamorphosis of the precocious child runs parallel. Occasionally, the excretion level for one of the hormones may be normal, but in our experience none has been found to be below normal in this type of patient. Assay for the sex hormones are of value in differentiating precocious puberty from similar syndromes produced by neoplasms or hyperplasia of endocrine organs. In the latter abnormalities, particularly those of the adrenal glands or gonads, the hormone excretion levels are usually very high. Furthermore, except when the primary lesion stimulates pituitary secretion, it is unusual to find elevated excretion levels of each of the hormones. For example, tumors of the adrenal cortex, especially carcinoma, give rise to a marked elevation of excretion of the 17-ketosteroids and estrogens, particularly the former, whereas the granulosa cell tumor of the ovary is usually associated with a marked increase in the excretion of estrogens alone, without apparent change in the 17-ketosteroids. An increase in pituitary gonadotropins would be unusual with either type of tumor. Intracranial neoplasms producing pubertas praecox offer the greatest diffulty in differential diagnosis from those syndromes in which no definite etiologic factor can be ascertained. As far as we can tell hormone excretion rates in this type of neoplasm are only slightly higher or may easily fall into the range of the cases reported in this section. Moreover, there is usually an elevation of the excretion levels of the pituitary gonadotropins, 17-ketosteroids, and estrogens because the primary stimulation is probably of the anterior pituitary gland. Therefore, the clinical syndrome of precocious puberty, coupled with a knowledge of the sex hormone excretion rates, should aid materially in a diagnosis of the site and nature of the primary lesion.

Retarded growth and development. In contrast to precocious puberty, these syndromes may be due to hypofunction of the anterior pituitary or of the gonads, or of both organs. Hypofunction of the anterior pituitary gland usually results in decreased excretion levels of gonadotropic hormones, estrogens and 17-ketosteroids. However, failure to recover urinary gonadotropins implies, but does not necessarily prove pituitary hypofunction since our present methods may not be adequate to recover smaller amounts. On the other hand, primary gonadal deficiency in the presence of normal gonadotropic function may give rise to an elevation in the excretion of the gonadotropins. Depending upon the sex of the individual, the excretion rates of the estrogens or 17-ketosteroids are depressed. This may be explained by the concept that the gonadotropic hormones stimulate only the gonads and have no apparent direct effect upon the adrenals. Cases of individuals having primary ovarian insufficiency associated with decreased stature and high urinary gonadotropin titers have been reported previously (10, 11). In this present series, a male, *case 15*, may fall into the category of primary gonadal hypofunction. Thus, it seems that the variations in excretion rates of the various hormones may depend upon which of the glands is primarily deficient in function. Primary pituitary hypofunction may be differentiated from end organ deficiencies in some instances by the injection of potent gonadotropic extracts (*case 26*). Subsequent to such therapy, an increase from low levels of 17-ketosteroid excretion in the male and of estrogen excretion in the female may indicate an ability of the gonads to respond to a proper stimulus and the failure of the pituitary gland to provide such a stimulus. Failure to respond to the stimulus may signify gonadal deficiency with or without hypofunction of the pituitary.

Adiposo-genital dystrophy. It is commonly held that this syndrome may occur as a result of dysfunction of the pituitary gland. The levels of sex hormone excretion in this study confirm this point of view. Pituitary gonadotropic hormone was not recovered in any untreated patient. The 17-ketosteroid levels were usually below average in the male, but about normal in the female. The estrogens, however, were normal or slightly above normal in every male, but in the one female, *case 31*, the excretion was considerably below the average range for her age and sex. This suggests that the gonadotropic function of the anterior pituitary was decreased, thus resulting in a diminished excretion of the urinary 17-ketosteroids in the male and the estrogens in the female. Since there is evidence

that the adrenals produce substances which are excreted in the urine as estrogens and 17-ketosteroids it seems reasonable to postulate in view of the retarded sexual development that the excretion levels of the hormones in these cases represent largely the secretion of the adrenal glands rather than the gonads. However, this does not imply that there is an inability of the gonads to respond to a proper stimulus for in *case 26* the injection of gonadotropic hormone was followed by a significant rise in 17-ketosteroid excretion. Adiposo-genital dystrophy seems to differ primarily from cases with retarded growth and puberty of pituitary origin, in the degree of somatic development. Thus, each syndrome may represent a different type of pituitary dysfunction. This seems to be borne out clinically since in the case of retarded growth and puberty there is a delay in skeletal and gonadal development, whereas in adiposo-genital dystrophy there is a deficiency in the gonadal development with an associated obesity.

Relationship of bone age, bone or somatic growth, chronologic age and the excretion of the sex hormones. Conclusions with regard to growth rate are dependent upon the accuracy of normal standards. We have used as standards the most recent figures of Stuart (12) for children up to 72 months, and those of Meredith (13) and Boynton (14) for the older child. A careful distinction must be made between bone age and bone growth for the former is an indication of the development, metamorphosis and maturation of bones, whereas the latter merely implies an increase in length and diameter. Therefore, they should be considered separately since some of our observations indicate that bone age and bone growth may be dependent upon different factors. Our previous study has demonstrated that the levels of excretion of 17-ketosteroids in normal children are usually correlated more closely with the physical and skeletal development than with chronologic age (1). This is confirmed in these children in whom physical development and maturation deviate widely from the normal. The estrogen excretion level may also parallel physical development but there is not such a close association. In the female child the estrogen excretion levels correlate more closely with the degree of sexual development. An interesting example of this is furnished by *case 7* in whom the 17-ketosteroid levels correspond to the bone age and chronologic age whereas the estrogen levels, which were elevated, paralleled the rapid sexual development and somatic growth. A further study of these correlations may further differentiate the factors concerned with these various aspects of growth.

Sexual metamorphosis. It was discussed in another paper (1) that the higher estrogen excretion in the female and the higher 17-ketosteroid excretion in the male were probably due to the addition of the respective gonadal secretions to that of the adrenals. Since these hormones are probably responsible for and their excretion parallels the sexual metamorphosis in the normal child, these levels would be expected to correspond to the sexual age in the precocious or retarded child. The data confirm this viewpoint.

Estrogen—17-ketosteroid ratio. It is apparent that the excretion of estrogens, 17-ketosteroids and perhaps the gonadotropins, is correlated with the abnormalities of growth and development. The chief difficulty in the interpretation of these data lies in the lack of knowledge of the relationship of the estrogens to the 17-ketosteroids, for there are some cases in which the excretion levels of these two sex hormones are not equally distorted from the normal. Normal children of either sex at any given age show a rather constant relationship between the urinary levels of the hormones. Before the age of 9 there is little difference in either sex, but after this time the relationship changes in that the excretion levels of estrogens become progressively higher in girls and those of the 17-ketosteroids in boys (1). Alterations or exaggerations of this ratio are striking in certain types of tumors of the gonads or the adrenals, but in the cases reported here, with but few exceptions, the relationship remains constant regardless of the levels of the excretion. For example, in pubertas praecox not only the levels but the ratio correspond to that of an older normal child with whom the degree of development compares. Deviations from this ratio are found in the adiposo-genital syndrome in the male, in which there is a relatively lower level of the 17-ketosteroid excreted and, if any change, a somewhat elevated

estrogen excretion so that the ratio approaches that of the female. This is extremely interesting inasmuch as the body configuration also tends toward the feminine type. Such change in ratio appears to be of considerable importance in evaluating the physiologic response to these hormones. The evidence is too great to be ignored that in many respects the estrogens and androgens are antagonistic in their action both in animals and in man. Abnormal ratios, in our experience, have been associated with similar clinical deviations. It also appears obvious that the amount of hormone necessary to produce changes in the body is much smaller in early life than in the adult or senescent individual. This indicates a greater susceptibility in the growing organs to such a stimulus. The young organs respond to even a mild stimulation, while senescent organs behave as though they had become immune.

Possible etiologic factors in the production of these syndromes. The production of the above syndromes has been ascribed to a number of etiologic factors. The acute exanthemata with a possible accompanying encephalitis have been listed as the more common causes, but developmental defects such as internal hydrocephalus and malformations within the brain have also been reported. In a surprisingly large number of our patients there was a history of onset following exanthemata, particularly scarlet fever and mumps, although there was no good evidence that there was an accompanying encephalitis.

SUMMARY

Children were studied because they showed deviations from the normal rate of growth and sexual development. Analysis of urinary excretion rates of pituitary gonadotropins, estrogens, and 17-ketosteroids indicates that these rates are correlated with the extent of metamorphosis rather than with the chronologic age of the child.

The importance of these relationships and their use in the differential diagnosis and prognosis, and as an aid to treatment is discussed.

We are indebted to Miss Lois E. Towne and Miss Rita Kelley for technical assistance; to the Children's Hospital of Boston for the privilege of studying four of their patients, cases 1, 2, 8, and 23; to Dr. R. Wagner for case 9, and to Dr. G. J. Rubin for case 5.

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ADDENDA

Since this paper was submitted for publication, an article on the 17-ketosteroid excretion in normal and abnormal children has appeared: Talbot, N. B., A. M. Butler, R. A. Berman, P. M. Rodriguez and E. A. MacLachlan. *Am. J. Dis. of Child.* 65: 364, 1943. The interesting monograph, "Somatic and Endocrine Studies of Puberal and Adolescent Boys," has also just been received by Greulich, W. W., R. I. Dorfman, H. S. Catchpole, C. I. Solomon and C. S. Culotta. Vol. VII, Ser. No. 33, No. 3. Monographs of the Society for Research in Child Development—National Research Council, Washington, D. C., 1942. Both of these investigations are in essential agreement with the work presented here.

Gonadotropin Excretion in Normal Men and Women and Cases of Hysterectomy, Menopause, Migraine, Epilepsy and Eunuchoidism

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THERE HAS NOW accumulated considerable evidence concerning the urinary gonadotropin excretion of human females and males. The following study, although not offering many new data, may serve to corroborate the accepted results, especially since a somewhat different technic from that often employed has been used.

METHOD

The technic of concentration is modified from that of Frank (1) and involves acidification to pH 5 and precipitation with 4 volumes of alcohol of the first morning specimen, dialysis of the precipitate through cellophane for from 4 to 6 hours in the cold (or more recently, washing with 80% alcohol), and 9 injections (two daily) of the entire amount into a 21-day-old female rat. As an end point, the uterine weight is used. However, when this increases above 120 mg., the ovaries are also usually weighed, since the uterine weight soon reaches a plateau beyond which it cannot increase.

Although most of the curves shown were made from data obtained by procedures in which the technic of dialysis was utilized, lately we have, instead, washed the precipitate twice with 200 cc. of 80 per cent alcohol in water in order to remove the toxic salts. Sodium and potassium salts are much more soluble in 80 than in 95 per cent alcohol. This washing is followed by another with 200 cc. of 95 per cent alcohol and then with ether. More recently Varney and Koch (2) have shown that alcohol as dilute as 50 per cent may be used to diminish toxicity without loss of gonadotropic activity.

The rats are fed a stock diet without added NaCl, a separate supply of salt being available in the cage. Although we believe that it is the K salts which are most toxic (3) the animals undoubtedly tend to show some effect from the NaCl content of the injected solutions.

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RESULTS

Figure 1 represents the gonadotropin excre-

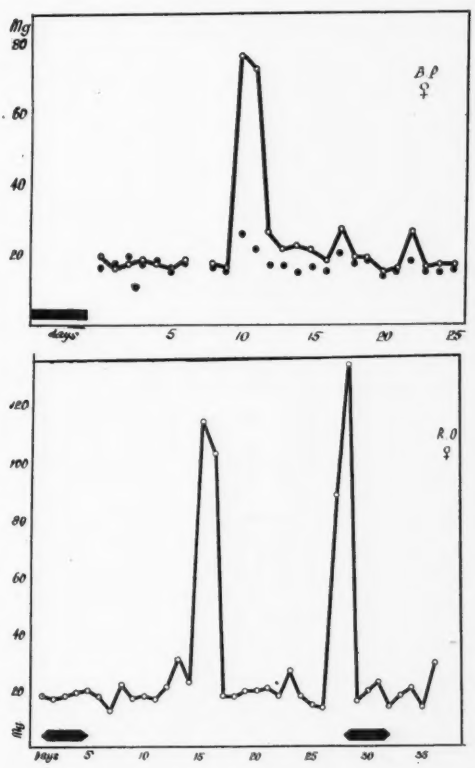

FIG. 1 (*upper*). Gonadotropin excretion in normal female; *solid line*, rat uterine weight; *black circles*, rat ovarian weight; *horizontal bars*, menses.

FIG. 2 (*lower*). Gonadotropin excretion in normal female; uterine weight in 21-day-old-rat.

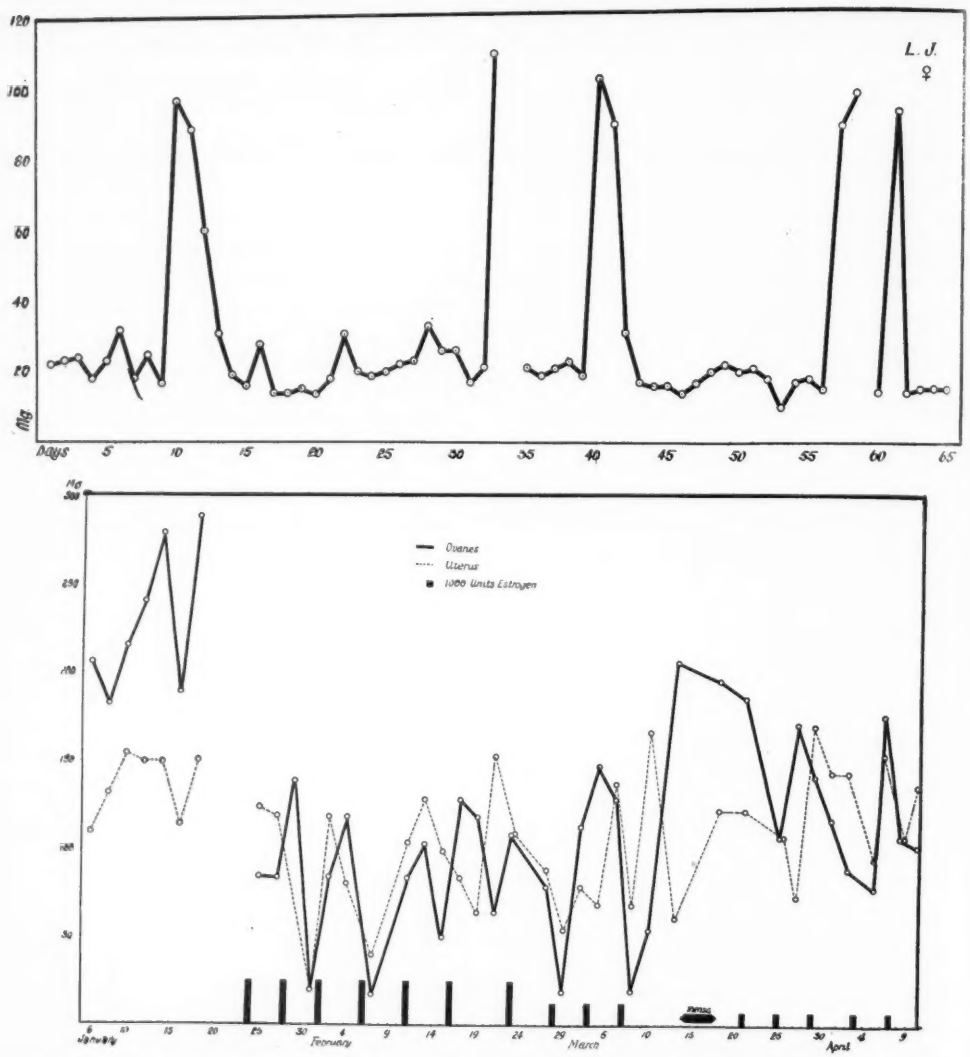

FIG. 3 (*upper*). Gonadotropin excretion in hysterectomized female; uterine weight in 21-day-old rat.
FIG. 4 (*lower*). Gonadotropin excretion in female with premature menopause. Reduction of amount of hormone excretion following estradiol benzoate, 10,000 R.U. per injection for 7 injections; less inhibition by 3 doses of 5000 R.U.; bleeding following temporary cessation of therapy with rise in excretion of gonadotropin; less inhibition with 5 injections of estradiol benzoate of 3000 R.U. each. *Solid line*, rat ovarian weight; *broken line*, rat uterine weight; *upright bars*, estrogen injections; *horizontal bar*, bleeding.

tion of a normal married female, 25 yeas old, and the curve corresponds to the single peaks obtained by this same technic in two other normal women (4, 5).

Figure 2 is the curve of gonadotropin excretion in a normal unmarried woman 24 years old. This is the first time we have obtained two peaks of gonadotropin excretion in a normal unmarried woman as reported by others.

Since no gonadotropin had been detected in the urine of a patient with congenital absence of the uterus and pseudo dysmenorrhea (6) and it was suggested that absence of the uterus might have been concerned, the curve in figure 3 was plotted from data obtained on a multiparous woman, 37 years of age, who had had a complete hysterectomy 2 years previously. Gonadotropin was present, being of the multiple

peak type as reported by Heller (7). This would indicate that the congenital absence of the uterus in our previous case probably was not associated with the lack of detectable amounts of gonadotropic hormone.

Figure 4 is that from data on a married nulliparа in her twenties who had not menstruated since she was 18. The excessive amounts of urinary gonadotropin indicate a premature menopause. The rat uteri often reached the plateau of maximal hypertrophy of about 150 mg.; the ovaries, in the earlier part of the study at times weighed as much as 300 mg. Following intramuscular injection of estradiol benzoate (10,000 R.U.) about every 4 days, the excretion of gonadotropin dropped markedly, the greatest effect occurring apparently several days after injection. This may be due to the time required for absorption and consequent delay in inhibition of the pituitary, or to the fact that the body fluids contain so much of the gonadotropic hormone that some time is required for its excretion. A painful mastitis was produced with this dosage of estrogen, which was then reduced to 5000 R.U. for 3 doses. Temporary cessation of treatment resulted in the first menses in years. Treatment was resumed at a dosage of 3000 R.U. which plainly produced less inhibition of gonadotropin excretion. Approximately the same dosage orally (1000 R.U. daily) of estradiol (not shown in the curve) produced even less

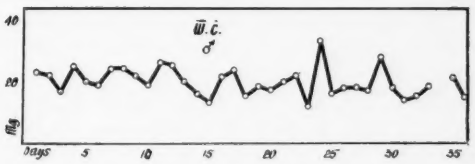

FIG. 5. Gonadotropin excretion in normal male; uterine weight in 21-day-old rat.

effect. This would suggest that this method might be useful to compare the relative efficacy of various estrogens given orally and parenterally. Our results agree with the generally accepted statement that an estrogen dosage, which is adequate to afford clinical relief, is usually far from enough to inhibit markedly gonadotropin excretion.

Figure 5 is that obtained in the case of a normal male aged 25 years, and figure 6 is from the data on gonadotropin excretion of a male,

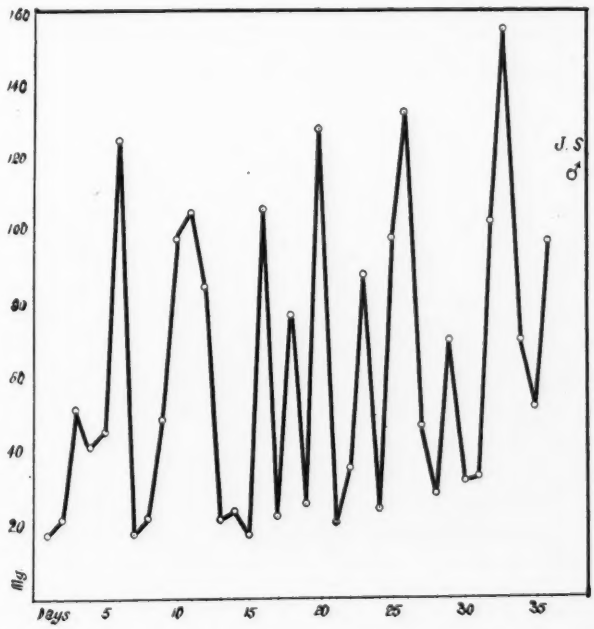

FIG. 6. Gonadotropin excretion in male with migraine; uterine weight in 21-day-old rat.

24 years old, who suffered from attacks of migraine, averaging one a week. Not realizing at at the time the relationship between migraine and urinary gonadotropin (8), no record was kept of the frequency of the migraine. Following dietary treatment as suggested by Foldes (9), the patient has had no further attacks for over a year, and does not excrete measurable quantities of gonadotropin. Moreover, the marked diuresis usually following the migraine has also disappeared. This hormone excretion should be kept in mind when using gonadotropin excretion as an index of testicular tumors in the male and also might explain the irregular excretion of gonadotropin reported in some females. Migraine was not a factor in the high level and irregular excretion rate of gonadotropin of a female being treated for hypothyroidism (10) who has since become pregnant in spite of the abnormal gonadotropin excretion.

Because of the aphorism that *migraine is epilepsy of the autonomic system, and epilepsy is migraine of the cerebral cortex*, the gonadotropin excretion of a 42-year-old male epileptic showing degeneration was studied for 10 successive days. Large amounts of gonadotropin were found, the uterine weights being consistently over 100 mg., reaching a maximum of 150 mg. The ovarian weights were 50 mg. and above, reaching a maximum of 115 mg. However, two other young male epileptics who were having occasional convulsions were studied over a period of 20 days each, without finding any distinct amount of hormone, the uterine weights only occasionally reaching a maximum of 35 mg. All 3 patients were receiving phenytoin therapy.

A 40-year-old male with all of the characteristics of eunuchoidism excreted no appreciable amounts of gonadotropin over a period of 10 days. His medical history was not clear; an operation had been performed at an early age, which may have been castration, or an unsuccessful attempt to remedy cryptorchidism. Lack of hormone in this case would indicate primary pituitary failure.

SUMMARY

A normal young woman had a single peak of urinary gonadotropin between menses, and another young woman, two peaks. A hysterectomized woman had normal single and double peaks in corresponding periods. A young woman with premature menopause has a constant high urinary titer of gonadotropin, which was reduced in proportion to the dosage of estrogen, suggesting a means of estrogen assay in the human female. A normal male had no appreciable excretion of gonadotropin; one with migraine showed a high and irregular level of excretion which disappeared with successful dietary treatment. One epileptic male excreted large amounts of gonadotropin but two others excreted none. A eunuchoid male did not excrete any demonstrable amount of gonadotropin.

We are indebted to Drs. Nathan Bloom, L. X. Kolipinski, S. G. Page, and P. H. Drewry for their co-operation and assistance; to Dr. William Rhea Bond of Schering Corp., Bloomfield, N. J., for the supply of estrogen; and to Mr. H. E. Stoeckle for assistance.

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Metabolic Changes in a Patient with Addison's Disease following the Onset of Diabetes Mellitus[1]

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THE DEVELOPMENT of diabetes mellitus in a patient with pre-existing Addison's disease has been reported only once (1).[2] There are, however, 11 well-documented instances in which diabetes mellitus and Addison's disease have developed simultaneously or in which the onset of diabetes mellitus has antedated the onset of Addison's disease. In 4 of the 11 patients, Addison's disease and diabetes mellitus appeared to develop simultaneously (table 1). In the remaining 7 instances the onset of Addison's disease appeared to follow the development of diabetes mellitus (table 2).

The case reported by Arnett in 1927 (2) has been referred to (11) as the first substantiated instance of the co-existence of the two diseases. A survey of the literature, however, revealed a case report by Unverricht in 1926 in which Addison's disease developed in a known diabetic (7). The case described by Crook and Russell in 1935 (13) had been reported in 1932 by Levy-Simpson (3) and hence these reports represent a single instance of the co-existence of the two diseases. Allen in 1930 (14) stated that only two patients with both diseases were encountered among 115 cases of Addison's disease and 3000 diabetic patients seen at the Mayo Clinic. No details were given in this paper, but it is to be presumed that the two cases referred to were those subsequently reported by Rowntree and Snell in 1931 (8, 9) in their monograph on Addison's disease. Mention might also be made at this time of a report by Brookfield and Corbett (15) concerning a diabetic patient who was observed at postmortem examination to have bilateral adrenal atrophy and fibrosis. Blood pressure determinations were not recorded and abnormal pigmentation was not noted. This patient was admitted to hospital in severe diabetic coma and died 12 days later. Umber (16) reported the cases of 2 elderly diabetic patients who later developed what was thought to be Addison's disease. Neither of these two patients displayed any evidence of decreased insulin tolerance. The data presented are meager, and insufficient to warrant the inclusion of these two patients among the well-established cases of diabetes mellitus and Addison's disease.

Of the 7 patients with well-established diabetes mellitus, 5 showed a definite decrease in the severity of the diabetes following the onset of symptoms of Addison's disease. It is well known experimentally (17, 18, 19) that re-

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[1] This study was aided in part by a grant from the Committee on Research in Endocrinology, National Research Council.

[2] This patient was a 32-year-old housewife who, at the time of onset of diabetes mellitus in June, 1940, had manifested the classical signs of Addison's disease for more than one year. During this period she had been maintained in good condition on 5 mg. of desoxycorticosterone acetate injected intramuscularly 3 times weekly. The onset of diabetes occurred rapidly and was marked by polydipsia, polyuria and weight loss. A glucose tolerance test gave the following values (mg. per 100 cc.): Fasting blood sugar level, 460; one-half hour, 480; one hour, 575; one and a half hours, 600; two hours, 565. She was given regular insulin, the dosage being gradually increased to a maximum of 38–0–22 units daily. The patient did well on regular insulin, and the maintenance dose subsequently fell to 28–0–20 units daily. In August, 1940, nineteen weeks after the onset of diabetes, she received an overdose of insulin while at home. She was brought to the hospital in a severe hypoglycemic reaction and despite the administration of intravenous glucose and adrenalin she expired. The etiology of diabetes mellitus in this patient was presumed to be familial. In the diagram the members of her family with diabetes are indicated with solid circles, whereas the nondiabetic members are indicated by open circles.

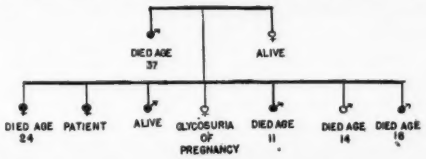

TABLE 1. PATIENTS WITH SIMULTANEOUS ONSET OF DIABETES MELLITUS AND ADDISON'S DISEASE

Author	Patient's Age	Sex	Duration of Diseases, Years	Pathological Findings Adrenal Glands	Insulin Requirement
Arnett (2) (1927)	39	F	3	atrophy	20–50 units daily
Levy-Simpson (3) (1932)	16	M	1	atrophy	10 units resulted in hypoglycemia
Gowen (4) (1932)	54	F	1.5	atrophy	5 units resulted in hypoglycemia (diabetes controlled by diet)
Koepf and Bowen (5) (unpublished)	20	M	2	atrophy	no insulin (diabetes controlled by diet)

TABLE 2. PATIENTS WITH DIABETES MELLITUS WHO SUBSEQUENTLY DEVELOPED ADDISON'S DISEASE

Author	Patient's Age	Sex	Duration of Diabetes at Time Addison's Disease Developed, years	Apparent Etiology of Addison's Disease	Duration of Addison's Disease	Daily Insulin Requirements, units: Prior to Onset of Addison's Disease	Daily Insulin Requirements, units: After Onset of Addison's Disease
Unverricht (6) (1926)	32	M	6	tuberculosis	2–4 months	40	5
Rowntree-Snell (7) (1931)	25	M	1	atrophy	15 months	0	20–30
Rowntree-Snell (8) (1931)		M	6	atrophy	18 months		
Rogoff (9) (1936)	25	M	4	denervation of adrenals	12 months	48–60	5–10
Bloomfield (10) (1939)	30	M	1	atrophy	(patient alive)	40	8
Bowen, *et al.* (11) (1942)	76	F	10	tuberculosis	12 months	0	improved glucose tolerance test
McCullagh (12) (1942)		M	7	atrophy	(patient alive)	40–120	40–50

moval of the adrenals modifies the course of diabetes in pancreatectomized or phlorhizinized animals.

The onset of diabetes mellitus in a patient with Addison's disease who had been intensively studied and who had received adrenal cortical hormone therapy over a period of 4 years prior to the development of diabetes provided a unique opportunity to investigate in man the nature of the modifying effect which these two diseases are thought to exert on each other.

PROTOCOL

J.H.H., (Johns Hopkins Hospital No. 160819, Peter Bent Brigham Hospital No. 62915), a 23-year-old white male, was admitted to the Johns Hopkins Hospital on Jan. 30, 1939, complaining of weakness, loss of appetite and discoloration of the skin. The present illness had begun during the winter of 1938 when the patient (then 22 years of age) first noted slowly increasing weakness. In May, 1938, headache and marked anorexia developed rather abruptly. At the same time generalized darkening of the skin became manifest. The patient was found to have a persistent low-grade fever and subsequently developed general glandular enlargement. He was admitted to a hospital where a diagnosis of Addison's disease was made. The typical blood picture of infectious mononucleosis was observed and the heterophile antigen agglutinations were found to be positive in dilutions of 1:64. The administration of large quantities of sodium chloride and adrenal cortical extract resulted in considerable improvement. He remained in fair health except for an acute attack of serum sickness in August, 1938, following an injection of tetanus antitoxin, when his temperature rose to 105°F. and he became comatose and went into shock. Following the administration of intravenous sodium chloride and glucose solutions and large amounts of adrenal cortical extract he made a rapid recovery.

The family history and the patient's past history were noncontributory. There was no familial history of diabetes mellitus.

Physical examination on admission Jan. 30, 1939, revealed a thin, but well-developed, rather tired young man, not acutely ill. The temperature was 98.6°F., pulse 84 per minute, respiratory rate 18 per minute and blood pressure 92/50 mm. Hg. He weighted 63.2 kg. (139 lb.). The skin was deeply tanned over the entire body with numerous black freckles over the back. Some bluish mottling was present along the gum

margins. The thyroid was not remarkable and the lymph nodes were not enlarged. The lungs were clear and examination of the heart revealed no abnormalities except a blowing systolic murmur at the apex. The liver and spleen were not palpable. The remainder of the physical examination was not remarkable.

The laboratory findings were as follows: Hb. 93 per cent; red blood cells, 4.5 millions; packed red blood cell volume (hematocrit), 41 per cent; white blood cells, 9700; polymorphonuclears, 47 per cent; lymphocytes, 43 per cent; monocytes, 9 per cent; and eosinophiles, 1 per cent. There were numerous abnormal lymphocytes resembling those seen in infectious mononucleosis. The blood Wassermann reaction was negative. The following blood chemical determinations were noted at this time: plasma sodium, 126.7 m.eq.; chloride, 95.2 m.eq.; and potassium, 8.2 m.eq. per liter; blood nonprotein nitrogen, 55 mg. per 100 cc.; and blood sugar (fasting), 83 mg. per 100 cc. Urine examination revealed a specific gravity of 1.020, a very faint trace of albumin and no sugar. The sediment contained an occasional red and white cell, but no casts. Roentgenograms of the chest and abdomen revealed no abnormalities. The basal metabolic rate was −1 per cent.

The patient was maintained on supplementary sodium chloride medication and daily injections of desoxycorticosterone acetate in oil. He showed remarkable improvement; the blood pressure increased to 110/70 mm. Hg, and he gained 2.5 kg. (5.5 lb.) in weight. After 12 days of desoxycorticosterone acetate therapy, the following blood determinations were recorded: packed red blood cells (hematocrit), 25.3 per cent; plasma sodium, 136.9 m.eq.; chloride, 105.6 m.eq.; and potassium, 6.2 m.eq. per liter; blood nonprotein nitrogen, 31 mg. per 100 cc. The fasting blood sugar at this time was 80 mg. per 100 cc. After the requirement for desoxycorticosterone acetate had been determined, crystalline pellets of the substance were implanted subcutaneously.

During the following 3 years the progress of the patient was followed carefully; he returned to the Johns Hopkins Hospital regularly for check-up and for re-implantation of pellets. Between 1938 and the spring of 1942 18 fasting blood-sugar determinations were recorded; all were within normal limits. In addition, two intravenous glucose tolerance tests were performed. During this 3-year period the patient was noted to become rather negativistic and at times almost catatonic following moderately prolonged fasting; administration of carbohydrate improved his disposition within a period of a few minutes. As a consequence of this, the patient was encouraged to take frequent feedings; by choice he ate an unusually high proportion of carbohydrate. Aside from occasional minor intercurrent respiratory infections, the patient was maintained in relatively good health until the fall of 1942. In the spring of 1942 the requirement of desoxycorticosterone acetate was estimated as being not over 3 mg. daily.

In September, 1942, following a mild upper respiratory infection, the patient failed to eat regularly. He lost weight and strength rapidly and developed increasing anorexia, lassitude and loss of ambition. The systolic blood pressure fell to 70 mm. Hg from a level of 135–145 mm. Hg. Following administration of adrenal cortex extract, desoxycorticosterone acetate in oil and saline solution parenterally by his local physician, the patient was sent to the Peter Brigham Hospital on October 4, 1942. Physical examination at this time differed from the original examination 4 years earlier in the following particulars: the pigmentation, while still generalized, was considerably lighter in shade. Blood pressure on admission was 98/74 mm. Hg. Generalized lymphadenopathy was present, with many discrete, shotty 'raisin-sized' nodes palpable in cervical regions, axillae and groin. Laboratory data on this admission disclosed the following: Hb., 93 per cent; red blood cells, 4.4 millions; white blood cells, 5300 with a normal differential. Urinalysis on admission (obtained following intravenous glucose and saline) showed a 3+ sugar. No further urinalyses were performed. Blood chemical findings were as follows: sugar, 212 mg. per cent; serum chloride, 100 m.eq.; carbon dioxide combining power, 27 m.mol. per liter; and blood urea nitrogen, 11 mg. per 100 cc. Standard metabolic rate was −17 per cent. While in the hospital, the patient's hormone requirement was re-assayed, and on Oct. 7, 1942, 5 pellets of crystalline desoxycorticosterone acetate were implanted subcutaneously. The patient's blood pressure gradually rose to 120/84 mm. Hg and the weight to 62.4 kg. (137.3 lb.). The blood sugar of 212 mg. per 100 cc., noted following admission, was assumed to be a laboratory error since on all examinations during the preceding 4 years the fasting blood sugar values had been normal. A second blood glucose determination made in an effort to correct the previous 'error,' was reported as being 309 mg. per 100 cc.!

Following discharge from the hospital, the patient was able to resume his normal activities. One week later, however, he developed a sore throat. Because of this, he was referred to a local hospital where he was given sulfadiazine and supplementary adrenal cortex and desoxycorticosterone acetate in oil. The patient was noted to have glycosuria and ketonuria. The acute infection subsided in 24 hours, but because of the persistent glycosuria and ketonuria he was re-admitted to the Peter Bent Brigham Hospital for diabetic study.

Physical examination at this time was essentially unchanged from that of the previous admission, except that the pharynx disclosed slight granular injection and the previously noted cervical lymphadenopathy was more marked. Blood pressure at this time was 130/70 mm. Hg. Laboratory data on admission disclosed the following: urinalysis, 4+ sugar, no acetone; Hb., 83 per cent; red blood cells, 4.2 millions; white blood cells, 4500 with a differential of 33 per cent neutrophils, 4 per cent eosinophils, 51 per cent lymphocytes, 6 per cent monocytes and 6 per cent atypical monocytic cells with toxic granules in cytoplasm. Heterophile antibody reaction was negative in all dilutions. The blood chemical findings at the time of admission

TABLE 3. DEVELOPMENT OF DIABETES MELLITUS IN A PATIENT WITH ADDISON'S DISEASE (PATIENT J.H.H.)

	1942				1943					
	Jan.	July	Oct. 4	Oct. 13	Nov. 2	Nov. 15	Dec. 2	Jan. 8	Feb. 4	Mar 15
Body weight (kg.)	72.0	71.0	61.4	60.4	61.0	60.2	62.2	64.6	68.0	69 0
(lb.)	158.4	156.2	135.0	132.9	134.2	132.4	136.8	142.1	149.6	151 8
Blood pressure (mm. Hg)	134/70	125/65	110/70	106/62	110/60	110/76	124/80	110/60	124/80	128/88
Desoxycorticosterone acetate requirement (mg. per day)	2.5	2.5	2.5	7.5	7.5	6.5	5.5	4.5	4.0	3.0
Supplementary sodium chloride (gm. per day)	0	2	3	6	0	0	0	0	0	0
Insulin dosage (units per day)					10	20	25	18	18	18
					Diagnosis of diabetes mellitus treatment instituted					

were: sugar, 338 mg. per 100 cc.; nonprotein nitrogen, 23 mg. per 100 cc.; total protein, 5.4 mg. per 100 cc., (albumin, 2.3 gm.; globulin, 3.1 gm.); cholesterol, 195 mg. per 100 cc.; chloride, 99 m.eq., and carbon dioxide combining power 21 m.mol. per liter. Twenty-four-hour ketosteroid excretion was 2.6 mg.

METHODS

During this study, the patient was fed a diet of standard composition (protein 83 gm., fat 112 gm., carbohydrate 220 gm. The caloric content of this diet was 2220). The standard diet was given for at least 2 days prior to each test period. On the day preceding glucose tolerance tests or studies of respiratory metabolism, the patient was given a relatively small dose (8 units) of regular insulin with his morning meal; no further insulin was administered until the following day, after completion of the test.

For a period of several weeks prior to these studies the patient was trained for respiratory metabolic studies. On each test day, following a 13-hour fast, expired air was collected for a 10-minute period in a Collins chain-compensated gasometer. Air samples were analyzed in duplicate for carbon dioxide and oxygen content on a Haldane-Henderson gas analyser. Standard metabolism was calculated; urinary nitrogen excretion was determined; and differential derivation of calories was carried out with the aid of Lusk's table (20). A standard intravenous glucose tolerance test (21) was made before and after the administration of 33 mg. of 11-dehydro-17-hydroxycorticosterone. During the test periods the daily urinary excretion of glucose, acetone, nitrogen (Kjeldahl), phosphorus (22), potassium (23), sodium (24) and chloride (25) were determined. Blood-sugar determinations were made according to the method of Folin-Malmros (26).

TABLE 4. FASTING BLOOD-SUGAR VALUES, MAY, 1938, TO FEBRUARY, 1942, PATIENT J. H. H.

	1938	1939	1940	1941	February 1942
Blood sugar, mg. per 100 cc. (average and range)	90	87	95	89	88
	78–102	80–100	93–98	81–100	82–93
Number of determinations	9	8	5	4	2

OBSERVATIONS

The onset of diabetes mellitus in this patient with Addison's disease previously well controlled with synthetic desoxycorticosterone acetate therapy, was characterized by progressive and unexplained anorexia, weakness, weight loss, fall in blood pressure and increased hormone requirement (table 3). A review of laboratory data collected during the 4 years preceding the onset of diabetes revealed no significant increase in fasting blood-sugar values during this period (table 4). The period of 1938–1942 was characterized by frequent bouts of spontaneous hypoglycemia which occurred particularly during the course of intercurrent infections, following prolonged fasting or following strenuous exercise. This patient, however, did not have a hypoglycemic episode precipitated by the administration of intravenous glucose as so frequently occurs in patients with Addison's disease (21). It is noteworthy that the glucose curve in 1939 and 1940 (fig. 1) returned to normal somewhat more slowly than is usually the case in normal subjects and in patients with Addison's disease. A progressive decrease in glucose tolerance was

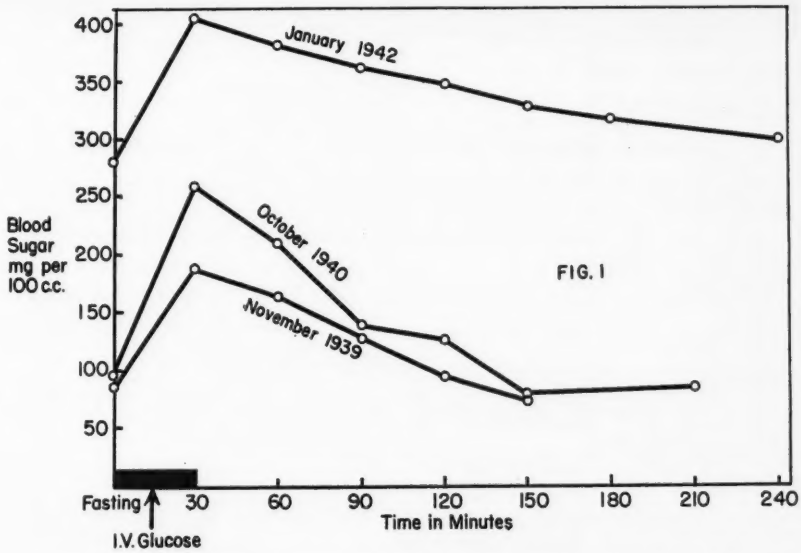

FIG. 1. Intravenous glucose tolerance tests in Addison's disease (*patient J. H. H.*). 0.5 gm. of glucose per kg. of body weight.

observed between 1939 and 1940 (fig. 1). The onset of diabetes mellitus was associated with a further decrease in glucose tolerance (1943). During the years 1938 to 1942, this patient subsisted on a diet which was almost exclusively carbohydrate, although not exceptionally high in calories.

On admission to the Peter Bent Brigham Hospital, Oct. 4, 1942, the patient was found to be dehydrated and to have a moderate decrease in blood pressure (table 3), although the size and number of pellets of synthetic hormone implanted subcutaneously appeared to be adequate. During the initial period of dehydration prior to admission to the hospital ketonuria had been observed. With supplementary injections of desoxycorticosterone acetate in oil[3] rehydration occurred and a rise in blood pressure followed. At this time spontaneous ketonuria was minimal or absent despite the continued excretion of rather large quantities of glucose (50–100 gm. daily). It appeared that ketone production exceeded ketone utilization in this patient with Addison's disease and diabetes mellitus only during periods of severe dehydration or during the course of intercurrent infections.

The striking effect of insulin treatment of blood-sugar levels and renal excretion of glucose, nitrogen, phosphate and potassium is demonstrated in figure 2. Insulin withdrawal was accompanied by an increase in glucose excretion and presumably an increase in glucose formation from endogenous protein sources as evidenced by the increased excretion of nitrogen, phosphorus and potassium. Ketonuria did not occur. Blood-ketone determinations were not made.

Insulin sensitivity was especially noteworthy in this patient as illustrated by the following episode. After determining that the fasting blood-sugar level was 350 mg. per 100 cc., 10 units of insulin was administered, following which a breakfast containing carbohydrate 88 gm., protein 23 gm. and fat 44 gm. was given. At noon 5 units of insulin was given prior to a lunch which contained carbohydrate 52 gm., protein 25 gm. and fat 31 gm. At 3:00 P.M. the patient was found to be in a stupor from which he could not be roused. Intravenous glucose administration resulted in prompt recovery. Thus despite a fasting blood-sugar level of 350 mg. and the administration of a total of 140 gm. of carbohydrate at breakfast and lunch, this patient developed hypogly-

[3] Desoxycorticosterone acetate in oil (Percorten) was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

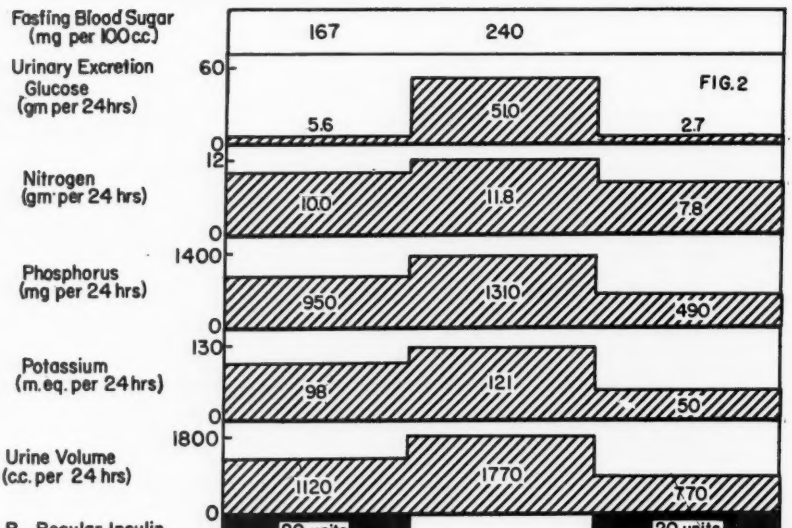

FIG. 2. Effect of insulin withdrawal on renal excretion of glucose, nitrogen, phosphorus and potassium (*patient J. H. H.*). Diet, gm.: carbohydrate, 220; protein, 83; fat, 117.

cemia following the administration of 15 units of regular insulin (10 units prior to breakfast and 5 units prior to lunch).

An interesting and unusual reaction occurred in this patient during the initial period of insulin administration and following large supplementary injections of desoxycorticosterone acetate and supplementary sodium chloride medication. This was characterized by a rapidly developing paralysis of the muscles of both lower legs and feet. There was no pain and no evidence of disturbance in sensation or reflexes. A provisional diagnosis of 'low-potassium paralysis' was entertained, and appeared to be confirmed by the low level of serum potassium which was observed at that time (3.46 m.eq. per liter) and by the striking improvement which followed administration of potassium citrate. Paralysis of this nature has been observed in a patient with Addison's disease who was treated with excessive doses of desoxycorticosterone acetate and supplementary sodium chloride following nephrectomy (27) and in normal dogs receiving large doses of desoxycorticosterone acetate (28). It is possible that in this patient the shift of potassium from the serum following insulin administration in the presence of a high blood-sugar level (29, 30) may have augmented the effect of excessive desoxycorticosterone acetate and sodium chloride therapy.

A marked improvement in appetite followed the institution of insulin therapy. Prior to the development of diabetes this patient's appetite had been poor and finical. He had consumed, by choice, a diet composed almost entirely of carbohydrate; the maintenance of an adequate protein intake had been a major problem. Following the onset of diabetes, however, the appetite increased and he displayed a fondness for fatty foods. His weight increased approximately 10 kg. (22 lb.) in 5 months.

The development of diabetes mellitus in this patient was accompanied by a dramatic alteration in personality and outlook on life. During the 4 years prior to the onset of this complication, he had been noted to be a taciturn, shy, introverted individual who intentionally limited his contacts with strangers and new situations to the barest possible minimum. His withdrawal had been noted to be most marked following prolonged fasting, at which times he became definitely negativistic and almost catatonic in attitude. Since the onset of diabetes mellitus, however, he has overcome to a considerable extent his avoidance of challeng-

ing situations. Whereas in the past it had been difficult to arouse or hold his interest in any activities not directly relating to himself, he now displays a moderate degree of spontaneous enthusiasm.

Despite the continued high levels of blood sugar, this patient's abnormal electro-encephalographic pattern (31) has not revealed significant improvement. It is possible that in this patient the maintenance of a high blood-sugar level without normal capacity to utilize glucose may be a factor in perpetuating the abnormalities previously observed. It is also possible of course that the changes previously reported may be permanent in nature. It is of interest to note that the improvement in psyche has not been reflected in a measurable alteration in electro-encephalographic pattern.

During the course of the illness, slight changes in the configuration of the electrocardiogram of this patient have been noted. These have been interpreted as of no clinical significance, however, and have shown no relation to the onset of diabetes mellitus. Heart size, as measured by the teleoroentgenogram, has varied with the patient's clinical state and hormone level, but has shown no significant alteration since the onset of diabetes.

Changes Accompanying the Administration of 11-Dehydro-17-Hydroxycorticosterone (Compound E, Kendall)

The administration of a single dose of 33 mg. of 11-dehydro-17-hydroxycorticosterone[4] (compound E, Kendall) in oil was followed by a striking decrease in glucose tolerance as measured by the intravenous glucose tolerance test (fig. 3). A balance study made during the period of compound E administration revealed a marked increase in glucose, nitrogen and phosphorus excretion (fig. 4). It is also of interest to note that there was an increase in sodium and chloride excretion with compound E treatment (32). No increase in potassium excretion was observed (fig. 4), whereas a striking increase in potassium excretion accompanied insulin withdrawal (fig. 2). A decrease in respiratory quotient and a striking change in basal caloric distribution was induced by the administration of compound E (fig. 5). These changes have been compared (fig. 5) with those observed in a patient with uncomplicated Addison's disease and a normal human subject treated with the same quantity of compound E (33 mg.). In all 3 individuals there was a rise

[4] Kindly supplied by Dr. E. C. Kendall of the Mayo Clinic, Rochester, Minnesota.

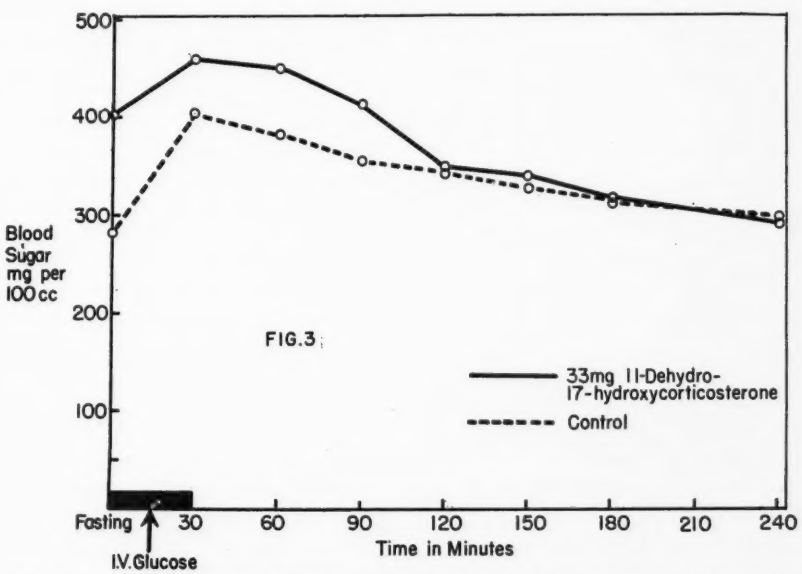

FIG. 3. Effect of 11-dehydro-17-hydroxycorticosterone on intravenous glucose tolerance (*patient J. H. H.*). 0.5 gm. of glucose per kg. of body weight.

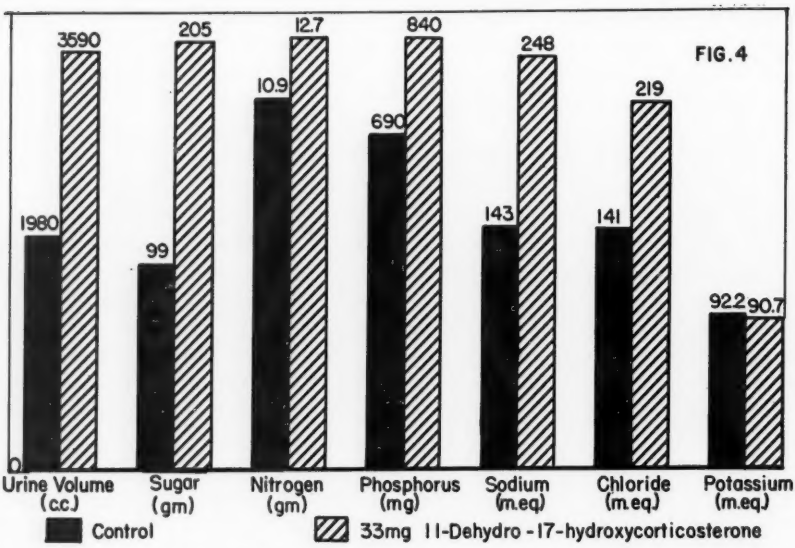

FIG. 4. Effect of 11-dehydro-17-hydroxycorticosterone on 24-hour renal excretion (*patient J. H. H.*). Diet, gm.: carbohydrate, 220; protein, 83; fat, 117. Regular insulin, 8 units daily.

in fasting blood-sugar level and a striking decrease in fasting nonprotein respiratory quotient. In both patients with Addison's disease there was a definite increase, following the administration of compound E, in basal oxygen consumption. This change did not occur in the normal subject (fig. 5).

DISCUSSION

A unique opportunity to study the mechanism of the alterations of carbohydrate metabolism in Addison's disease and diabetes mellitus was presented by the development of the latter disease in a patient with Addison's disease who had been under careful observation for a period of 4 years. The earliest evidences of a diabetic trend in this patient were *a*) maintenance of normal fasting blood-sugar values, and *b*) failure to develop hypoglycemia following intravenous administration of glucose (21). Later there was definite evidence of decreased glucose tolerance as indicated by the blood-sugar curve following glucose administration (fig. 1, year 1940).

It has been suggested (17, 18) that the development of spontaneous hypoglycemia in the absence of adrenal cortical hormone results from an impairment of gluconeogenesis. Furthermore, the relatively high nonprotein respiratory quotient in patients with Addison's disease suggests an impaired ability to utilize fat (21). In the presence of combined diabetes mellitus and Addison's disease, however, it appears that utilization of fat is not impaired, as at least 60 per cent of basal calories were derived from fat in this patient on several occasions. Despite the relative severity of his diabetes, ketonuria in this patient was minimal at all times as long as hydration was maintained with adequate desoxycorticosterone acetate therapy. It cannot be stated whether the absence of ketonuria reflected decreased ketone formation from fat and protein or increased ketone utilization with or without an increased renal threshold for ketone bodies. Rather severe ketosis has been reported in several of the cases of concurrent diabetes mellitus and Addison's disease (1, 2, 3). A review of the data presented, however, revealed that ketonuria was observed only in the presence of dehydration or intercurrent infection.

The development of diabetes mellitus in this patient enabled him to maintain high blood-sugar levels during prolonged fast; therefore, it would appear that the inability of patients with uncomplicated Addison's disease to maintain an adequate blood-sugar level cannot be explained entirely on the absence of adrenal cortical hormone, since increased gluconeogenesis was observed without any increase in

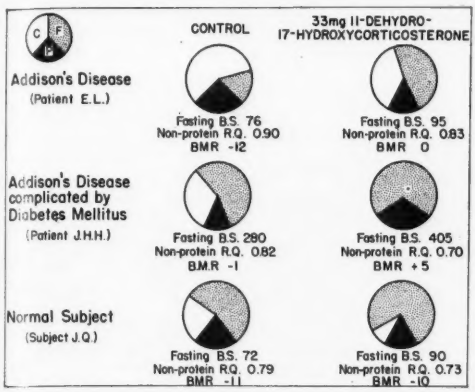

FIG. 5. Effect of 11-dehydro-17-hydroxycorticosterone on fasting blood-sugar level and caloric distribution.

adrenal cortical hormone when diabetes supervened.

The alterations in metabolism observed in this patient following the administration of 33 mg. of compound E confirm the observations of Ingle and Thorn (33) on the action of adrenal cortex preparations containing an oxygen atom on C. 11. The marked increase in fasting blood-sugar levels and increased renal excretion of nitrogen and phosphorus observed following administration of this substance (fig. 4) suggests that it initiates increased gluconeogenesis. The alteration in the glucose tolerance curve following compound E administration suggests that this compound also inhibits glucose utilization or storage. A marked increase in the 24-hour renal excretion of sodium and chloride occurred. Potassium excretion, on the other hand, was not altered. It is possible that the unchanged renal excretion of potassium following compound E therapy reflected the neutralizing effect of two antagonistic actions of this hormone, *a*) the increased rate of potassium liberation from protein break-down, as evidenced by increased excretion of nitrogen and phosphorus, and *b*) the possible action of the hormone in increasing the renal tubular re-absorption of potassium. In addition to promoting increased gluconeogenesis, compound E treatment appeared to alter fat metabolism in this patient. Fasting respiratory metabolism studies indicated that a marked lowering of nonprotein respiratory quotient occurred, and that the percentage of calories derived from fat increased significantly (fig. 5). A considerable degree of ketonuria was present following compound E therapy, whereas otherwise it was minimal or absent.

Because of the high degree of insulin sensitivity which this patient presented it was felt that the administration of protamine zinc insulin might be unwise. With the use of regular insulin, it was possible to delay insulin administration until immediately prior to beginning a meal. Another mechanism which protected this patient against excessive administration of insulin was the return of his negativistic attitude when the blood-sugar level was low. As a conquence of this, he refused to take or to be given any medication (including insulin) at this time, whereas he was perfectly willing to do so when the blood sugar was higher and his disposition consequently more amiable.

SUMMARY

A second case of diabetes mellitus developing in a patient with well-established Addison's disease has been described. The onset of diabetes mellitus in this patient with previously well-controlled Addison's disease was characterized by anorexia, loss of weight, lassitude, fall in blood pressure and increased requirement of desoxycorticosterone acetate. Institution of insulin therapy at a time when large doses of desoxycorticosterone acetate and sodium chloride were being administered precipitated the development of 'low potassium' muscular weakness. Regulation of diabetes with small doses of insulin was followed by striking improvement in appetite, desire for fatty foods, increased weight, restoration of blood pressure and general sense of well-being. Marked improvement in personality was observed in conjunction with the persistent hyperglycemia. No change in the abnormal electro-encephalogram was noted. Withdrawal of insulin was followed by an increased blood-sugar level, and an increased excretion of nitrogen, phosphorus and potassium. With adequate desoxycorticosterone acetate, which prevented excessive dehydration, no return of ketonuria was observed during the aggravation of diabetes induced by insulin withdrawal. The marked insulin sensitivity of this patient suggests that protamine zinc insulin administration might prove to be extremely hazardous. The administration of a single dose of 33 mg.

of 11-dehydro-17-hydroxycorticosterone was followed by an elevation in blood-sugar level, a lowering of nonprotein respiratory quotient, increased excretion of glucose, nitrogen and phosphorus accompanied by the presence of ketonuria and increased excretion of sodium and chloride. It appears from studies on this patient that the inability of patients with uncomplicated Addison's disease to maintain an adequate fasting blood-sugar level is not dependent solely upon deficiency of the adrenal cortical hormone.

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Diabetes Mellitus Associated with Hirsutism and Unusual Insulin Resistance

CASE REPORT

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THE ASSOCIATION in women of diabetes mellitus and beards was first described by Achard and Thiers (1) in 1921. Since that time much interest has developed in clinical pictures displaying these among other symptoms, and considerable controversy has arisen concerning the etiologic factors underlying these findings. The following case report not only demonstrates the problems in diagnosis but unusual features in carbohydrate tolerance as well.

CASE REPORT

Mrs. J.L.E., a 58-year-old Jewish widow, para 0-0-0, was first seen in the Metabolic Clinic of Charity Hospital on Sept. 17, 1937. The presence of glycosuria and a blood sugar of 275 mg. per cent led to a diagnosis of diabetes mellitus. The patient was regulated on 20 units of regular insulin once daily, but the insulin requirements, as denoted by glycosuria and hyperglycemia, gradually rose until, in 1940, the patient was taking a total dosage daily of 260 units of crystalline insulin. She was then changed to a combination of protamine and crystalline insulin totalling 190 units daily. Later she was maintained on the unusually high dosage of 195 units of protamine insulin daily, which was continued until she was admitted to the hospital on March 16, 1942, for re-evaluation of the virilizing syndrome and of the diabetes mellitus. Throughout this period in the clinic she was maintained on a diet of 1330 calories with 150 gm. of available glucose. Persistent glycosuria and frequent mild acetonuria were noted, but no symptoms of diabetic acidosis ever developed. The decreasing carbohydrate tolerance, as determined by standard glucose tolerance tests, is graphically shown in figure 1, which reveals the progress of the diabetes mellitus in the period from 1940 to 1942.

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At the time of admission to the hospital on March 16, 1942, the patient (fig. 2–4) manifested virilism, hypertension, plethoric facies, obesity confined chiefly to the torso, amenorrhea, genital regression—all of several years' duration—and diabetes mellitus which, as noted above, had been observed for 5 years. Family history, developmental history and past history were non-contributory. Menarche ocurred at 18 years; periods were regular every 28 days, with 3 days of scant flow. Dysmenorrhea had occurred occasionally on the day preceding onset of menstrual flow. Menopause occurred at the age of 35, presumably of physiologic origin. The patient was married at the age of 32. Libido and sexual compatibility were apparently present. No pregnancies resulted. Her husband was killed when the patient was 44 years old. The patient stated that she had always been chubby and short and that some hirsutism dated since early childhood. She shaved her face two or three times weekly and, in her opinion, the degree of hirsutism had not deepened recently. Patient did not tire easily, perspired freely and had oily hair. She had never taken any endocrine preparations other than insulin.

A general endocrine survey was made. The patient was a short, obese, white female of age 58. A blood pressure of 140/80 mm. Hg was recorded. At times it reached 190/100. The obesity was symmetrically distributed with a tendency to greater distribution on the trunk than on the extremities. Skin was moderately oily and of a reddish hue, but was judged to be of normal texture and consistency. The thyroid gland was slightly palpable. Considerable hirsutism was present on lips, face, trunk, back, sacral area and extremities. A definite pubic escutcheon of the masculine type was noted with a ridge of coarse black hair extending to the umbilicus. The hair in general was wiry, dark and luxuriant in growth. No striae were noted. Breasts were poorly developed with considerable fatty tissue and scant glandular tissue. The vaginal and rectal examinations revealed the pubic hair as described above, very small labia minora, dry, non-succulent vaginal mucosa, partially atrophic vaginal canal ad-

mitting one finger with ease, small, freely movable cervix and uterine body, and normal adnexa. The clitoris was not hypertrophied.

In an effort to demonstrate an etiologic basis for the above manifestations, the following studies were instituted: lateral view of the sella turcica, visual fields and eye grounds, roentgen views of skull and vertebrae for evidences of osteoporosis, chest film, basal metabolic determinations, excretory urography, peri-renal insufflation. No abnormalities were revealed. Basal metabolic determinations varied from +10 to +14. Blood cholesterol was 232 mg., urea 15.7 mg.; CO_2 combining power of the blood ranged from 42 to 56 vol. per cent on 11 consecutive determinations. Urinalysis showed glycosuria and occcasional mild acetonuria, but revealed no evidences of kidney impairment. Hematologic studies were within normal limits. No hormonal titrations were made.

A series of metabolic observations concerning the diabetes mellitus were recorded and all insulin was discontinued. At that time the patient was taking 195 units of protamine zinc insulin daily. The diet of 1330 calories was continued. There was very little effect from the discontinuation of the insulin. During the following 12 days, the patient spilled 1+ and 2+ sugar qualitatively. On March 28, 1942, the diet was increased to 174 gm. of available glucose with 1610 calories and maintained at that level for the remainder of her stay in the hospital. Whereas traces of acetone had been noted three times during the preceding 12 days, the increase in diet resulted in a more frequent positive reaction for acetone without clinical acidosis, accompanied by a 3+ and 4+ reaction for glucose, especially before the noon meal. The early morning specimen of urine usually manifested a 1+ reaction for glucose.

In view of the presence of disturbed carbohydrate metabolism and the lack of a definite etiologic basis for the clinical picture, roentgenologic therapy to the pituitary gland was considered. Throughout the period from April 6 to April 27, 1942, the patient received a total of 2400 r. applied through two lateral portals. A glucose tolerance curve was established prior to the irradiation and repeated at the conclusion of therapy (fig. 1). At the conclusion of the roentgenologic treatment, no change was noted in the daily glycosuria but acetonuria had been definitely reduced to an occasional trace of acetone at intervals of once every 2 or 3 weeks. No untoward clinical reactions were observed.

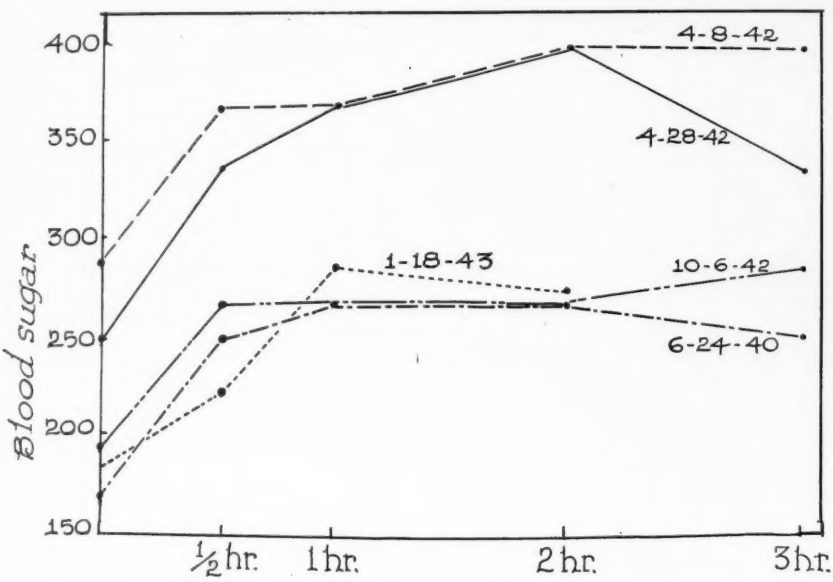


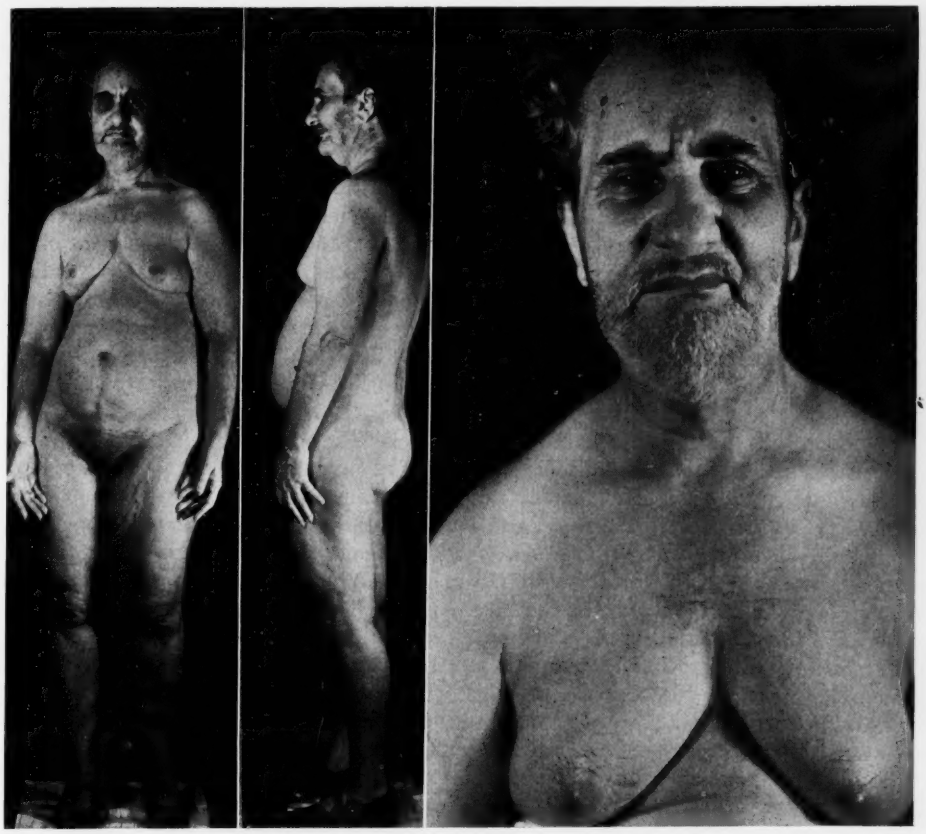
FIG. 1. Standard glucose tolerance tests in 58-year-old woman with diabetes mellitus, virilism and resistance to insulin.

On April 30, 1942, the patient was discharged from the hospital on a diet of 1610 calories and no insulin.

The patient has been seen at periodic intervals in the Metabolic Clinic since that date. Glucose tolerance curves were repeated on Oct. 6, 1942, and on Jan. 18, 1943. Acetonuria has been very infrequent but mild glycosuria has been recorded on frequent 24-hour-urine specimens. On Oct. 6, 1942, the patient's diet was increased to 200 gm. of available glucose with 1940 calories daily and has been at that level to this time. Her weight is now stabilized and the patient feels clinically well.

DISCUSSION

The data derived from this patient fulfill present-day criteria for the diagnosis of frank



FIGS. 2, 3, 4. Appearance of 58-year-old woman with diabetes mellitus, virilism, plethoric facies and obesity confined chiefly to the trunk.

diabetes mellitus. However, the rôle of malfunction of many organs, especially the hypophysis, thyroid, liver, and adrenals as well as the pancreas, in the disturbance of carbohydrate metabolism which is interpreted as diabetes mellitus, demands an evaluation of the diabetic patient from the standpoint of evidence of disease in these organs.

In 1932 Cushing (2) described the syndrome commonly called pituitary basophilism. The clinical characteristics of this syndrome, as described by Cushing, are as follows: a rapidly acquired and often painful obesity limited chiefly to the face, neck and trunk, but usually sparing the extremities, producing the so-called 'buffalo type' of obesity; cervico-dorsal kyphosis, occasionally with a decrease in stature; regression of the sexual organs in women with associated amenorrhea, sterility and loss of libido; hirsutism, in particular on the face and trunk, resembling somewhat a masculine distribution of hair; a dusky, plethoric appearance of the skin, often with purplish striae on the lower part of the abdomen and medial aspects of the thighs, and occasionally accompanied by acrocyanosis and ecchymosis of the extremities; facial changes which make the eyes appear small and slit-like, producing the so-called 'pig eyes'; hypertension; polycythemia; glycosuria; osteoporosis, particularly of the vertebrae, resulting in vague lumbosacral pains; and, if the carbohydrate tolerance is sufficiently disturbed, the clinical features of diabetes mellitus, such as fatigability and muscular weakness, polyphagia, polyuria, polydipsia, hypercholesterolemia, dryness of skin, and visual disturbances resulting from alterations in water balance. Two of the 14 verified cases reported by Cushing (3) occurred in men.

Although this syndrome has been widely rec-

ognized, its cause is determined with difficulty and, in individual cases, it is frequently impossible to establish the etiologic factor. Cushing (2) believed that this typical syndrome was associated with basophilic adenomata of the pituitary gland. Pardee (4) noted hyperplasia instead of adenomata, and Fuller (5) observed the association of the syndrome with a chromophobic adenoma of the pituitary. Susman (6) discovered non-clinical basophilic adenomata of the pituitary in 3 per cent of routine autopsies.

Moehlig and Bates (7) advanced the theory that the primary pathologic disturbance existed in the adrenal cortex and that basophilic infiltration in the pituitary gland was secondary. Indeed the clinical features of the syndrome have been related to adenomata, carcinomata and hyperplasia of the adrenal cortex by Turney (8), by Kepler and group (9), by Hare and associates (10), by Calder and Porro (11), by Oppenheimer and co-workers (12) and others. The studies of Long (13) and others have shown that the adrenal cortical hormone promotes gluconeogenesis and the conversion of proteins into sugar. From these observations, Albright and co-workers (14) suggest that the diabetes mellitus of Cushing's syndrome may be ascribed to hypergluconeogenesis.

Although Calder and Porro (11) attached significance to hypertrophy of the clitoris as being suggestive of the adrenal form, Oppenheimer and Silver (15) concluded that there were no clinical findings by which patients with Cushing's syndrome due to pituitary basophilism could be distinguished from those in whom the syndrome was due to adrenal cortical involvement. Metabolic studies have yielded few significant data. Hormonal titrations of blood and urine have been investigated extensively, but, by themselves, do not permit accurate differentiation. In general, increased androgenic values (17-ketosteroids) of the urine accompany the syndrome (14, 16, 17, 18, 19, 20), the chief androgen excreted appearing to be dehydroisoandrosterone derived presumably from the adrenal cortex (20). The differential diagnosis of Cushing's syndrome has been reviewed in detail in a recent article by Dorfman, Wilson and Peters (16).

The present patient showed many of the findings characteristic of Cushing's syndrome—obesity, changes in the sex organs, hirsutism, plethoric appearance of the skin, hypertension, and a disturbed carbohydrate metabolism. Decalcification of bones, polycythemia, striae and severe hypertension are lacking Although the absence of the latter findings does not exclude the diagnosis of Cushing's syndrome, the incompleteness of the picture, together with the absence of evidence of enlargement of the pituitary or adrenal glands, makes the diagnosis a doubtful one. It is possible that in the future the patient may develop added findings which will make the diagnosis of Cushing's syndrome conclusive. Such evidence, or histologic study of the gland, would be necessary for final decision.

Virilizing phenomena may be related to other disturbances. Leyton, Turnbull and Bratton (21) observed such findings in a patient with carcinoma of the thymus. Silver (22) added pineal tumors. R. Meyer and others have emphasized the association of virilizing phenomena, without hypertension and metabolic disturbances, with arrhenoblastoma of the ovary. The present case does not seem to fit into any of these categories.

Hirsutism with or without obesity occurs in a considerable number of patients on the basis of hereditary or unknown causes. No hereditary factors were found in the case of our patient. Unknown causes undoubtedly include both adrenal and pituitary disturbances in which criteria for diagnosis are inadequate. The faulty carbohydrate tolerance favors such a possibility. Through the work of Houssay it is well known that the anterior pituitary gland may exert a marked influence on carbohydrate metabolism. Extracts of the anterior pituitary gland have produced diabetic states in normal experimental animals and anti-insulin activity has been found in the urine of patients with Cushing's syndrome with diabetes (23). Eosinophilic adenomata of the anterior pituitary are sometimes associated with diabetes mellitus.

A most interesting and striking finding in our patient is the effect of insulin on the disturbance in carbohydrate metabolism. The ability of this patient to receive 260 units of crystalline insulin daily without any particularly pronounced effect upon the carbohydrate metabolism and without the development of insulin reactions has been interpreted as a state of insulin re-

sistance. Just as striking was the lack of change in carbohydrate metabolism with discontinuation of the insulin. Unfortunately no insulin sensitivity test, such as described by Himsworth and Kerr (24), was made. These workers also found insulin insensitive types of diabetes in two patients with Cushing's syndrome. In one, roentgen irradiation of the pituitary region was followed by clinical improvement as well as improvement in the patient's sensitivity to insulin. Fraser, Albright and Smith (25) also found the hyperglycemia of Cushing's syndrome resistant to insulin therapy. Himsworth and Kerr noted further that insulin-insensitive patients fall, in general, into a clinical group different from that of the insulin-sensitive cases. Insulin-sensitive diabetic patients tended to be relatively young, thin, with normal blood pressure and arteries, easily developing ketosis and marked reactions to insulin. The insulin-insensitive group was older, obese, hypertensive and arteriosclerotic. They tolerated over-dosage of insulin well without hypoglycemic symptoms and rarely developed ketosis. Certainly our patient had these latter characteristics. Himsworth and Kerr interpreted their data on the glucose tolerance and the insulin glucose tests to indicate that insulin-sensitive diabetes resulted from lack of insulin while insulin-insensitive diabetes resulted, not from lack of insulin, but from impaired action of insulin. These patients have a number of characteristics in common with the obese 'diabetics' described by Newburgh (26).

The mechanism of insulin insensitivity is not understood. The possible rôle of the anterior pituitary gland has already been mentioned. The frequent development of insulin resistance with infection and other conditions (24) has led to the idea that endogenous insulin production by the pancreas is diminished. Greene, David and Johnston (27) have shown that this concept is not necessary for the explanation. They depancreatized dogs and stabilized them on diets and insulin. Varying degrees of insulin resistance developed from injections of bacteria, irritating substances, and, in one instance, spontaneously. Since no endogenous insulin was produced in these animals, endogenous insulin could not enter into the explanation of insulin resistance. A reduced effectiveness of insulin, mechanism not yet determined, obviously was the cause.

In instances in which the causative lesion cannot be definitely demonstrated for Cushing's syndrome, Freyberg, Barker, Newburgh and Coller (28) recommend irradiation of the pituitary gland, a view shared by Bromley (29) and others. As a result of our failure to demonstrate a definite etiologic basis for the syndrome in this patient and because of the possibility that pituitary disease might play a part in its development, roentgenologic therapy was applied to the pituitary gland. From a study of figure 1, it will be observed that a gradually increased impairment of carbohydrate tolerance existed in this patient throughout the period from 1940 to the time of admission to the hospital in 1942. The clinical demands for increasing dosages of insulin may be used partially to substantiate this view, although the insulin resistance interferes with this interpretation.

Following roentgenologic therapy to the pituitary gland, two observations by standard glucose tolerance tests in the past 10 months have revealed definite improvement in the carbohydrate tolerance. It is to be recalled that no insulin has been given during the past year. Qualitative and quantitative observations of glycosuria and acetonuria over this period of time have supported this assumption. Some of the improvement in the carbohydrate tolerance may have resulted from, or be related to, the fact that the patient experienced a considerable weight loss for 6 months following roentgenologic therapy, in spite of the fact that the diet had been increased gradually to 1940 calories from 1330 calories, which had been maintained throughout the preceding 5 years without effect on weight.

In the past 3 months, the patient's weight has been stabilized. It is not clear whether the weight loss resulted from direct improvement as a result of roentgenologic therapy to the pituitary gland or whether the sudden cessation of insulin may have prompted it. Evidence against the latter view is found in the fact that the carbohydrate tolerance, as measured by the glucose tolerance test, appears to be definitely improved. Additional objections to acceptance of the apparent improvement in the carbohydrate tolerance of this patient as a consequence of roentgenologic therapy of the pituitary gland lie in the facts that no definite diagnosis of pi-

tuitary basophilism can be established and that the diabetes mellitus is not cured, but only improved. Whether the patient would have manifested similar findings without any roentgenologic therapy to the pituitary gland, or whether additional roentgenologic therapy is indicated with the hope of further improving the carbohydrate tolerance, is conjectural. Certainly no other evidences of improvement of the findings other than carbohydrate tolerance and weight loss have been noted.

SUMMARY

A patient exhibiting hirsutism and disturbed carbohydrate metabolism has been presented with the purpose of emphasizing the protean picture of disease encompassed by these findings, the pluriglandular aspects of diabetes mellitus, a remarkable degree of insulin resistance and 'indifference,' and the apparent improvement in carbohydrate metabolism that may follow irradiation of the pituitary gland in carefully selected cases.

The authors wish to express their appreciation to Dr. Manuel Garcia of the Department of Radiology, Tulane University and Charity Hospital of Louisiana at New Orleans, for his kind cooperation in the roentgenologic therapy of this patient.

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Serum Phosphatase Activity in Hyperparathyroidism

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INTEREST in the metabolism of phosphorus and particularly the relationship of inorganic phosphate to phosphoric esters has been steadily increasing since Grosser and Husler (1) discovered that hydrolysis of such esters in the animal organism is governed by an enzymatic system.

Although phosphatase activity is exhibited by a variety of tissues, the greater part of investigative work has been centered on the rôle phosphatase plays in the metabolism of bone. It has been determined that the phosphatase involved shows optimum activity at pH 9 to 9.5, and thus might properly be termed alkaline phosphatase.

Quantitative phosphatase studies on tissue may be made by various means such as specific staining technique and tissue extraction. While such procedures permit excellent comparative studies on specific tissue, they are not generally adaptable for clinical laboratory work due to the inaccessibility of most of the tissues involved. However, marked variations in local phosphatase activity are commonly reflected in the phosphatase content of the serum, and its quantitative determination in whatever arbitrary units one may choose may be of considerable significance in the diagnosis of a number of clinical disorders.

It is interesting to speculate on the source of the phosphatase in serum. Bone most likely supplies the major part since an appreciable reduction does not occur after the removal of other organs containing phosphatase. Moreover, Robison (2) has found that phosphatase activity is high in growing bone and cartilage. Markedly increased osteoblastic activity may reflect itself in correspondingly increased phosphatase levels in the serum. Kay (3) and many other workers have recorded quantitative serum phosphatase determinations in a number of bone diseases, including metastatic carcinoma to bone from various organs.

Davies (4) demonstrated in liver and spleen the presence of a different phosphatase with an optimum pH of approximately 5. This phosphatase has been generally termed 'acid' in contradistinction to the 'alkaline' phosphatase previously observed. Its physiological action has not been definitely determined. Among other organs rich in acid phosphatase the prostate has assumed great importance since the discovery that disseminated carcinoma of this gland is frequently attended by high acid phosphatase levels in the blood. Huggins and Hodges (5) have used phosphatase determinations as a quantitative measure of neoplastic activity of prostatic cancer as affected by sex hormones. At the present time a serum-acid-phosphatase value exceeding 10 King and Armstrong units is usually considered diagnostic of carcinoma of the prostate with skeletal metastasis. It should be emphasized that significant increases in blood phosphatase do not occur while the neoplastic growth is confined within the gland itself.

In view of the high content of acid phosphatase in the normal prostate, it is logical to assume that the source of the increased acid phosphatase in blood in disseminated carcinoma of the prostate is metastatic prostatic tissue. That other sources of acid phosphatase in blood exist

is evident from the fact that it is present normally in small amounts. Gutman and Gutman (6) investigated acid and alkaline phosphatase activity in a number of miscellaneous diseases including many with marked elevation of alkaline phosphatase. In their series of cases only patients with carcinoma of the prostate with bony metastases exhibited high acid phosphatase in the blood.

Within the last year we have had the opportunity to study an 18-year-old girl suffering from hyperparathyroidism due to a solitary adenoma of a parathyroid gland. The diagnosis was confirmed by microscopic examination of the adenoma following its surgical removal. The alkaline phosphatase values in the serum were very high and increases in the acid phosphatase levels of a magnitude hitherto only reported in disseminated prostatic carcinoma were present. To be certain that the increases really represented a 'peak' in the acid range, we determined the phosphatase activity by the King and Armstrong (7) method at pH of 4, 5, 6, and 9.5.

The following values given in King and Armstrong units were found:

TABLE 1. PHOSPHATASE ACTIVITY IN SERUM OF PATIENT WITH SOLITARY ADENOMA OF A PARATHYROID GLAND

	pH[1]			
	4	5	6	9.5
Dec. 4, 1941	7.5	12.5	9.0	78
Dec. 8, 1941	Surgical removal of adenoma			
Dec. 18, 1941	8	15.5	5.5	129
Jan. 13, 1942	2.0	6.0	1.0	
Jan. 15, 1942	1.5	5.0	1.5	56
May 2, 1942		3.0		11

[1] The buffers used in the acid range were acetic acid-sodium acetate mixtures while the alkaline buffer was the original King and Armstrong sodium barbital solution.

This study shows that pathological conditions aside from disseminated prostatic carcinoma may produce considerable increases in the acid phosphatase activity in blood.

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Melanotropic Hormone and Vitiligo

Report of Eleven Cases

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The pituitary gland produces a melanotropic hormone which is responsible for the color of the skin in batrachians. This fact, together with the observation in 1937 of dyschromias in a number of cases of both hypopituitarism and hyperpituitarism[1] has led to the investigation of the possible effect of a melanotropic hormone on vitiligo.

Successful results were obtained in 1938 by the local application of the purified injectable preparation of the melanotropic hormone in a patient with vitiligo (1) and in 1941 in two more cases of vitiligo treated in the same manner (2).

The purpose of this report is to review these cases to which are added 8 additional patients.

The results of therapy were good in 5 of the 8 new cases and no appreciable change was noted in the remaining 3. The beneficial effects consisted of a striking reduction in the area of the leucoderma without complete restoration to normal. These patients are still under treatment.

Treatment was started by giving local intradermal injections, 400 frog units twice a week but the changes produced in areas of vitiligo remote from the point of injection showed that the hormone also had a general action at the dosage given.

CASE REPORTS

Case 1. J.M.B., male aged 18. Neither the family nor personal history was pertinent. Vitiligo was the chief complaint, the discoloration first appearing over the scrotum about 5 years ago, there being no emotional stress or other cause associated with it. Within 6 months other patches appeared at both wrists and later on the forehead near the hair line (fig. 1). Treatment was instituted with the melantropic hormone by intradermal injections twice a week at the left wrist. After 4 months the areas of discoloration on the forehead began to contract and a year after the institution of therapy had entirely disappeared (fig. 2). The other areas of vitiligo changed but little.

Case 2. A.E de M., female, aged 33. The family history was unimportant. The patient had been rather fat as a girl; as an adult the weight has been consistently about 80 kg. (176 lb.). The patient described nervousness and numbness about different parts of the body since she was 12 years old. She was first seen in the clinic late in 1941, (fig. 3) complaining of vitiligo over the face, chest and back and some scattered patches over the abdomen and legs. The patches first developed on the back 4.5 years ago; following this they appeared on the face, and shortly after on the chest, abdomen and legs. The melanotropic hormone was injected intradermally into the frontal patch twice a week for 4 weeks. Because of pain produced by this treatment one injection per week was made into the arm. The patches on the face soon began to disappear following therapy, and they are almost absent at present (fig. 4). The largest area of leukoderma on the back is now about one-half of its original size and the remaining patches have improved to the same degree.

Case 3. N.M., male, 50 years old. There was no family history of vitiligo. A sister and an aunt have diabetes. The personal history appeared irrelevant. Vitiligo was the chief complaint, discoloration having appeared suddenly about 3 years ago. No mention was made of actual emotional stress or worry. The disease ran a rapid course and within a week was established on the forehead, face and right side of the neck. A month later small patches began to appear on the body and limbs. The patient tried unsuccessfully several topical treatments for 7 months. He then came under our observation and therapy with the melanotropic hormone was instituted consisting of two weekly injections for 6 months, following which the patches on the face apparently improved. After two months the treatment was reduced to a single injection weekly. The patient has been so treated for 2 years and the areas involved have greatly improved, especially the patches on the face (fig. 5 and 6).

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[1] The authors mentioned the names of Marañon, Richet, Soudel, Netter and Barry, but gave no references.

Case 4, V.P., female, aged 15. The family history was unimportant. The patient was of a nervous disposition and reported an increased thirst and sweating, and a sensitivity to cold. She had flat feet. The patient has had vitiligo since the age of 5, when the disease first appeared on both knees with no apparent cause. Following this, it involved the skin over the ankles and finally of the groin by the time she was 8 years old. There has been little progression of the disease in the patch in the right cervical region. There is no history of emotional shock at the time. The whitish area remained unchanged for 4 years at the end of which time it began to increase in size while new ones appeared on the right side of the nape of the neck. Local intradermal injections of concentrated melanotropic preparation containing 2500 frog units per cc. were then given twice a week into the original patch which showed a slight decrease in size after the fourth injection. Following this, the area remained unchanged in size for 5 months in spite of constant therapy, although it developed a pinkish hue. Treatment was stopped for a month and then resumed at a dose of 400 frog units twice a week for 4 months. At present, however, no further improvement has been noted.

FIG. 1, 2. Case 1, aged 18. Vitiligo of 4 years' duration on forehead. Melanotropic hormone twice a week produced improvement within 4 months. Figure 2 made at end of 1 year of therapy.

FIG. 3, 4. Case 2, aged 33. Vitiligo of 4 years' duration; treatment with melanotropic hormone instituted. Figure 4 shows appearance of patient at present time.

FIG. 5, 6. Case 3, aged 50. Vitiligo of 3 years' duration. Melanotropic hormone therapy for 2 years. Figure 6 shows appearance of patient at present time.

last 7 years, with the exception of a few single patches on the hands, neck and angles of the mouth. Therapy with melantropic hormone was instituted nearly 2 years ago, about 120 treatments having been given during this time and consisting chiefly of local intradermal injections twice a week into the skin areas over the knees. These areas have improved in appearance; the small patch on the neck has disappeared and the tint of the few whitish areas still present is less intense. The disease as a whole has ceased to advance.

Case 5. Y.S., female, age 20. The patient has a sister, aged 16, with patches of vitiligo. Vitiligo first appeared in *Y.S.* at the age of 13 in the form of a small

Case 6. J.M., male, aged 40. The family and personal history were irrelevant. The patient has always been nervous. Vitiligo has been present for the last 11 years, having first appeared as small patches about the outer corner of both eyes. The skin over the genitalia and adjacent areas of the abdomen was involved about 5 years later. During the past 3 years vitiligo ha

also appeared on the lower limbs. At that time treatment with the melanotropic hormone was instituted at a dosage of 2 weekly injections of 400 frog units each; 50 injections were thus given into the arm, with some intervals of rest between the series. To date there has been no inprovement in the existing lesions, but no new patch has appeared during the 10-month period of treatment, and the vitiligo already present did not extend.

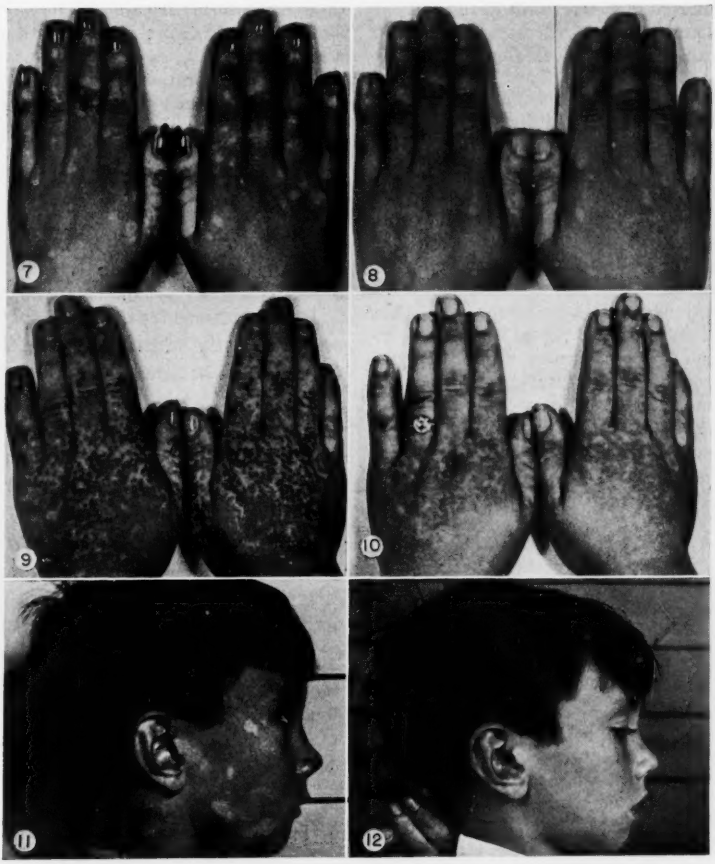

FIG. 7, 8. Hands of 26-year-old female with vitiligo of 5 years' duration. Treatment with melantropic hormone for 2 years. Figure 8 shows hands of patient at present time. Case 7.

FIG. 9, 10. Hands of 16-year-old female with vitiligo of 3 months' duration. Disease said to have appeared following severe attack of influenza. Figure 10 shows appearance of hands 4 months after institution of therapy with melanotropic hormone. Case 8.

FIG. 11, 12. Case 11, male, aged 7.5 years. Vitiligo of 2 months' duration. Figure 12 shows appearance after 10 months of treatment with melanotropic hormone. No relapse has occurred 4.5 years after cessation of therapy.

Case 7. S.C., female, aged 26. The patient gave a personal history of nervousness and irritability. Five years ago she first became aware of small discolored areas developing under the angles of the mouth. Areas of piebald skin subsequently appeared on the forearms, hands, neck, chest and abdomen. Both the onset and the rapid spreading of the disease for the last 3 years have had a background of emotional stress and strain. Treatment has been given for a year, consisting of two weekly injections of the melanophore hormone, 400 frog units each, into the inner aspects of both arms. The only positive result to be reported is a slight change about the patches on the hands (fig. 7 and 8). The vitiligo is no longer progressing.

Case 8. M.E.P., female, aged 16. The paternal grandmother had vitiligo. The patient sought medical advice because of vitiligo on the hands which was of 3 months' duration. A month after the onset of the disease patches began to appear also on the legs.

There was no connection with emotional factors. The statement was made that the disease followed a severe attack of influenza. Treatment was begun by ionization of the melanotropic hormone through the skin of both hands (3 weekly treatments with a current of 8 milliamperes for one-half hour). Apparent improvement was noted a month later. Therapy was continued for 3 months. The results of treatment in this patient can be seen in figures 9 and 10. Treatment was then discontinued because the patient left this country.

Case 9. O.C., female, 12 years old. The personal and family history were irrelevant. Vitiligo of 6 months' duration appeared coincidentally with the secondary sex characteristics. The patient exhibited a large patch on the right side of neck. There was another small area of vitiligo 2 cm. wide at the nape of the neck. Treatment was begun by giving two fresh bovine hypophyses daily and orally. Such treatment was continued for 14 months at the end of which time the cervical patch was approximately one-half of its former size, while the nuchal patch still persisted. Local intradermal injections of the melanotropic hormone were then given, 200 frog units once or twice a week for 20 months, during which time 94 injections were administered in all. Definite improvement was attained. The cervical patch became a small irregular blotch showing a number of tiny circular specks recently pigmented. The nuchal patch disappeared entirely.

Case 10. R.D. de U., female, aged 24. The family and personal history were irrelevant. Vitiligo in the past 7 years had spread almost over the entire body. The onset of the disease was associated with an intense emotional shock, its course was slow but increasing. The vitiligo suddenly became worse during the patient's only pregnancy, when it involved formerly healthy regions. The last patches to appear affected the face (chin and around both eyes). The melanotropic hormone was injected intradermally at a dose of 200 frog units twice a week with intervals of rest. The patient had a total of 72 injections in a year; these were always made into the same area of vitiligo (left elbow). A few months after starting therapy pigmentation occurred about the facial patches and continued steadily to the extent of changing the tinge of all of them. The relative effacement of the patches around the left eye can be seen in figures 15 and 16. Little change if any is apparent in the patches on the rest of the body the only difference being that they have become pinkish in hue and thereby offer a less marked contrast with the surrounding normal skin. Moreover the progress of developing vitiligo as a whole has stopped.

Case 11. D.R., male, aged 7.5 years. There was a history of diphtheria and polyneuritis at 2. The patient exhibited a right-sided facial vitiligo consisting of 5 patches of irregular outline which had appeared 2 months earlier (fig. 11). Intradermal treatment was begun with melanotropic hormone at a dose of 100 frog units twice weekly. There was an almost complete disappearance of the areas 5 months later (fig. 12) and vitiligo had entirely disappeared about 10 months after therapy was begun. At the present time, 4.5 years after restoration to normal, no relapse has occurred and the color of the skin at the site of original facial patches has remained unaltered.

SUMMARY

Treatment of vitiligo with the melanotropic hormone has proved successful as evidenced by the results in 8 of 11 patients thus treated (73%).

In one patient (*case 9*) fresh bovine hypophyses were orally administered; in 9 others a purified extract of the hormone was given either locally or subcutaneously.

The systemic action of such therapeutic measures is shown by the improvement of areas of vitiligo remote from the site of local intradermal injections.

On the basis of investigations on the electrical conveyance of the melanotropic hormone (3), local ionization was successfully tried once in our series (*case 8*).

Improvement has been more rapid and of greater degree in the patches which have appeared more recently. Satisfactory results, however, have been obtained in cases of vitiligo of 10 years' duration.

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Therapy of Seminal Inadequacy. II. Use of an Extract of Chorionic Gonadotropin and 'Pituitary Synergist'[1]

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EVANS and his associates (1–5) during the past 12 years have supplied evidence from their studies on the rat in particular that extracts of the anterior pituitary gland enhance the action of chorionic gonadotropin. They considered this enhancement of function to result from the operation of a true synergism and accordingly they have employed the term 'pituitary synergist' to describe this function of the pituitary. This group of workers in 1933 (5) reported that the so-called 'pituitary synergist' had been prepared sufficiently free from the gonad-stimulating and the growth-stimulating principles to render unlikely the possibility that these principles are responsible for this pituitary action.

There has been available commercially during the past year or so a preparation[3] which is said to be a 'balanced' combination of chorionic gonadotropin and the pituitary follicle-stimulating principle or the 'pituitary synergist' of Evans. The manufacturers state that in the preparation of their product the two fractions are obtained separately in highly purified form and that these are combined subsequently in proportions which are judged to yield maximum gonadotropic activity. This proportion is not defined. The unit of potency of this preparation (to be referred to henceforward as CG+PS) is the 'synergy rat unit' which is described to be 'the minimum total quantity, per rat, which, when injected subcutaneously, in equally divided doses, twice daily for three days into normal immature rats (26–28 days old, Wistar Strain) produces in that time an average ovarian weight five times that of untreated controls.'

Various reports (6–10) have described clinical experimentation with CG+PS in human females. Its preoperative use has been described (6) as having produced stimulation or overstimulation (accessory corpora lutea) in the ovaries of 20 to 23 patients. Despite the fact that this preparation has been described as promoting growth of the seminal epithelium and as stimulating androgenic elaboration by the interstitial tissue of the rat's gonads, no reports of its employment clinically in the therapy of seminal inadequacy have been encountered.

A previous report by members of our group (11) has described the nonoccurrence of significant improvements in the seminal values of 21 males with seminal inadequacy treated with various gonadotropins, including combined therapy with chorionic and pituitary gonadotropins. The present report deals with the results of treating 20 males with seminal inadequacy with CG+PS extract. Six of these 20 males had been treated previously with other gonadotropins, the results of these treatments having been reported in the previous communication.

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[1] The expenses of these studies were defrayed in part by research grants to one of us (E. C. H.) from Parke, Davis and Company, Detroit, Michigan, and from the Research Council of Duke University.

[2] Parke, Davis and Company Fellows in Clinical Endocrinology.

[3] Synapoidin, Parke, Davis and Company, Detroit, Michigan.

METHODS OF STUDY

The impaired seminal function of the 20 males treated was diagnosed during sterility surveys of them and their wives, made because of sterile mating, usually of two or more years' duration. Actual or impending military obligations of the husbands caused two couples, the durations of whose presumed sterility were only ½ and 1 year, to seek examinations.

In addition to seminal examinations, these males received endocrine and urologic surveys. All had basal metabolic rate determinations and roentgenograms of the sella turcica. Frequently, the levels of 17-ketosteroid excretion were established.

Seminal specimens were studied prior to, during, and after therapy. Adequate continence preceded the collection of specimens. All seminal fluids were collected directly and without the use of condoms. Examinations were made within 15 minutes to 1 hour after ejaculation.

Our seminal studies embraced the following examinations and the acceptance of the following values for normality: volume 4 cc.; immediate motility 80% to 95%; minimal count 60,000,000 per cc. or 240,000,000 for the entire ejaculate; and normal morphology 80% to 95%. For the purpose of analyzing and reporting our data, without the necessity of dealing separately with each of these factors, we have calculated the total number of motile spermatozoa per ejaculate (T.M.S.): the minimal limit for T.M.S. was considered to be 192,000,000. The calculation of a more satisfactory factor, the fertility index (total number of motile spermatozoa with normal morphology) is impossible at present due to the non-availability of suitable supra-vital stains. When significant morphological deviations occurred, and naturally these are not reflected in T.M.S., these are analyzed and reported separately in our data.

With one exception, at least two pretreatment seminal studies were made upon each patient. The total numbers of specimens studied per patient varied from eight to three, the average being five.

Therapeutic schedules embraced the daily intramuscular injection of 30 to 45 synergy units of CG+PS for four to twelve weeks, the average duration of a series of treatments being 5.7 weeks. The average total dosage of CG+PS per series was 1300 synergy units. Prior to any series of treatment, possible allergy of the patient to the preparation was investigated by intradermal skin tests. Respite from therapy equal in duration to the period of therapy followed each series of injections. A total of 27 series of treatments was given the 20 patients.

The period of observation of our patients with regard to this type of therapy varied from 3 to 18 months. Nine of these patients remain under observation and treatment.

When hypometabolism made advisable the use of thyroid protein or when hygienic errors or constitutional factors existed, seminal alterations incidental to appropriate adjuvant therapy were assessed before the gonadotropic schedules were initiated.

CLINICAL DATA

The ages of the patients ranged from 24 to 45 years. None of these exhibited signs of pituitary or androgenic deficiency. These were classified into three groups on the basis of physical findings:

Group I. Those with normal urogenital findings except for seminal inadequacy (cases 1, 7, 9, 12 and 22 to 29).

Group II. Those with partial atrophy of one or both testes but with no evidence of androgenic deficits (cases 13 and 30 to 32).

Group III. Those with chronic prostatitis and chronic epididymitis (cases 21 and 33 to 35).

The results of other gonadotropic therapies of patients 1, 7, 9, 12, 13 and 21 have been reported (11).

The pertinent clinical data of these 20 patients, including seminal assessments on the basis of total motile spermatozoa in the ejaculates, are summarized in table 1. Graphic presentation of the seminal findings and therapy of these patients in figures 1 to 6 provides data upon each seminal examination with regard to volume, morphology, immediate motility and number of spermatozoa per cc.

Data from seminal examinations made more than 18 days after the initiation of therapy and not more than 10 days following its cessation were considered treatment values. Those secured more than 10 days after the cessation of therapy and not more than 30 days after its cessation were considered immediate post-

TABLE 1. SUMMARY OF CLINICAL DATA ON 20 PATIENTS WITH SEMINAL INADEQUACY

Case Number	Age When First Seen, Years	Duration Presumed Sterility, Years	Pertinent Urogenital Findings	Average Pre-treatment Values			Average Treatment Values		Average Values Immediate Post-treatment		Average Values Delayed Post-treatment		Follow-up	
				Number, Sem. Exams.	Total Motile Sperms, Millions	Total Dosage CG+PS 'Synergy Units'	Number, Sem. Exams.	Total Motile Sperms, Millions	Number, Sem. Exams.	Total Motile Sperms, Millions	Number, Sem. Exams.	Total Motile Sperms, Millions	Wife Became Pregnant	Further Studies and Rx
Group I														
1	43	3½		2	2.6	2,670	3	T.F.C.[1]	1	2.5	2	11.1	No	Now
7	39	4		2	T.F.C.	1,050	1	T.F.C.					No	No
22	24	½		2	T.F.C.	1,260 1,260	1	aspermia	1	aspermia			No	Now
23	32	5		3	aspermia	1,890	1	aspermia			1	aspermia	No	No
9	32	5		2	5.6	840	1	0.1			1	1.0	No	No
12	31	2		1	148.7[2]	840 840	2	305.0[2]	1	92.0	1	48.4	Yes	
24	27	1		3	37.7	1,260	2	95.1					No	Now
25	30	14		5	70.8	1,260					1	48.9	No	No
26	29	2		2	96.0	1,470	2	24.4			1	26.0	No	No
27	30	4		2	7.2	1,260	2	34.4					No	Now
28	32	5		2	4.3	1,260 1,260	2	1.9			2	2.3	No	No
29	34	2		2	434.0[3]	1,260 1,260	1	463.0[3]	1	59.5			No	Now
Group II														
13	30	2	Right testis ½ normal size; left somewhat hypertrophied.	2	69.1	840 1,260	2	127.5			1	62.0	No	Now
30	45	2	Moderate atrophy of both testes.	3	2.1	1,260 1,890	2	2.0			1	2.7	No	Now
31	28	2	Right testis in inguinal canal; left somewhat hypertrophied.	2	5.6	1,260 1,260	2	0.08			1	1.3	No	Now
32	32	2	Failure of descent of right testis; left somewhat hypertrophied.	2	11.4	1,260	1	11.8					No	Now
Group III														
21	30	8	Chronic epididymitis.	4	31.7	1,260					1	5.9	No	No
33	31	3	Chronic prostatitis.	3	27.1	840	1	75.0			1	28.8	No	No
34	30	2	Chronic epididymitis.	2	aspermia	1,050	1	T.F.C.					No	No
35	45	12	Chronic epididymitis.	2	T.F.C.	1,680	2	T.F.C.					No	No

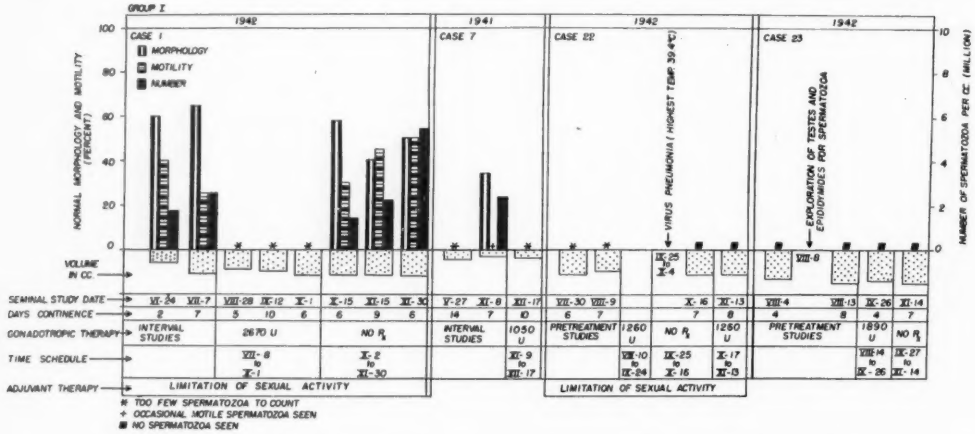
[1] T.F.C. indicates too few spermatozoa to count.
[2,3] Indicate instances in which the pathological seminal finding, i.e., decreased percentage of normal morphology, which occasioned therapy is not reflected in the formula T.M.S. (total motile spermatozoa).
[2] Corresponding pretreatment and treatment values for normal morphology in case 12 are 66% and 53%.
[3] Corresponding pretreatment and treatment values for normal morphology in case 29 are 68% and 62%.

treatment values. Those which were secured more than 30 days after the conclusion of therapy were considered delayed post-treatment values.

DISCUSSION

Reference to table 1, which is concerned with data on seminal values expressed in terms of total motile spermatozoa, indicates no consistent trend in the seminal values during treatment: of the 18 patients, concerning whom these values were available, those of eight were increased and those of five were decreased by varying amounts over pretreatment ones, while those of the remaining five were essentially not changed. The alterations observed in the treatment values of seven of the eight patients whose values were increased were generally small; the

factors for these increased treatment values in terms of the pretreatment ones were in order of magnitude: 4.77, 2.76, 2.52, 2.05, 1.84, 1.06 and 1.03. The only instance in which the T.M.S. rose sufficiently during therapy to warrant the assumption that the fertility of the patient had been altered significantly was that of the patient eight patients were decreased over the pretreatment ones, those of three were increased varying amounts while those of one patient were essentially unchanged. Delayed post-treatment values are available for four of the eight patients whose seminal values were increased during treatment: these values of three were decreased



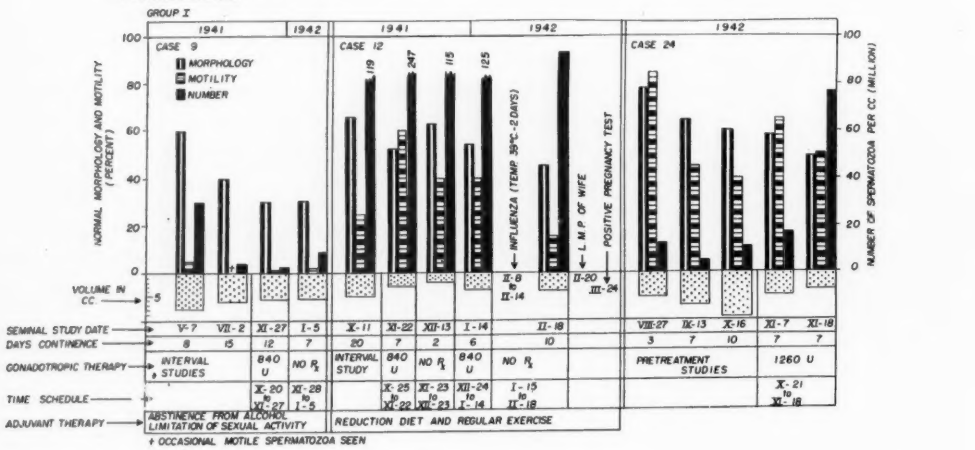


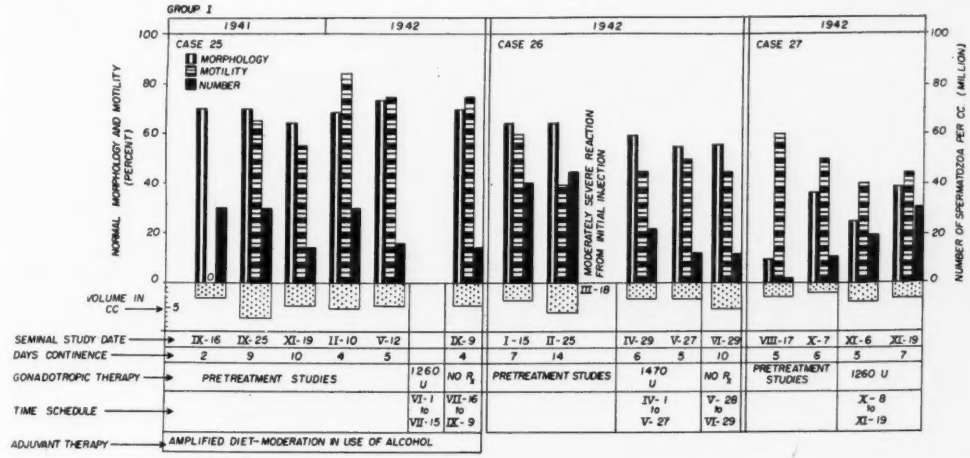
FIG. 1. Clinical data on cases 1, 7, 22 and 23.
FIG. 2. Clinical data on cases 9, 12 and 24.

in case 12, whose wife became pregnant despite a temporally associated marked drop in T.M.S. following discontinuation of therapy (figure 2).

Data, however, with regard to the end results of therapy, as judged by delayed post-treatment seminal studies, show a definite trend toward seminal values which are less than the pretreatment ones. Of the 12 patients concerning whom these data were available, values of while those of one were increased very slightly (T.M.S. 27.1 to T.M.S. 28.8).

No correlation was established between the physical status of the patients and their responses to therapy. Despite the fact that the 12 patients of group I were considered more likely to respond to therapy because of their non-possession of demonstrable urogenital pathology than the four patients of group II and the four

patients of group III, the observed improvements in seminal values did not bear out this assumption: four of the 12 patients (33%) of group I exhibited increased treatment values; two of the four patients (50%) of group II; and two of the four patients (50%) of group III.



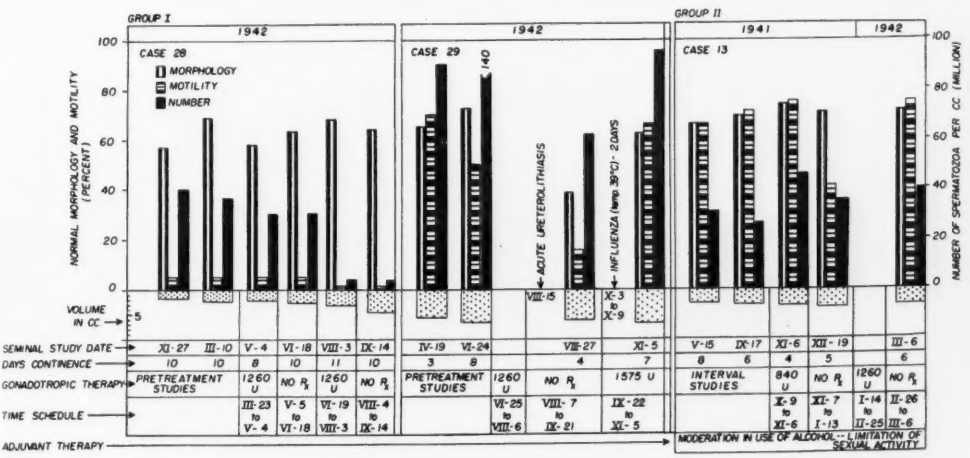


FIG. 3. Clinical data on cases 25, 26 and 27.
FIG. 4. Clinical data on cases 28, 29 and 13.

Figures 1 to 6 bear testimony to the fluctuations which occur spontaneously in the seminal values of the same individual prior to therapy and during therapy. These were frequently of essentially the same order under both conditions, a fact which renders recognition of significant improvements difficult.

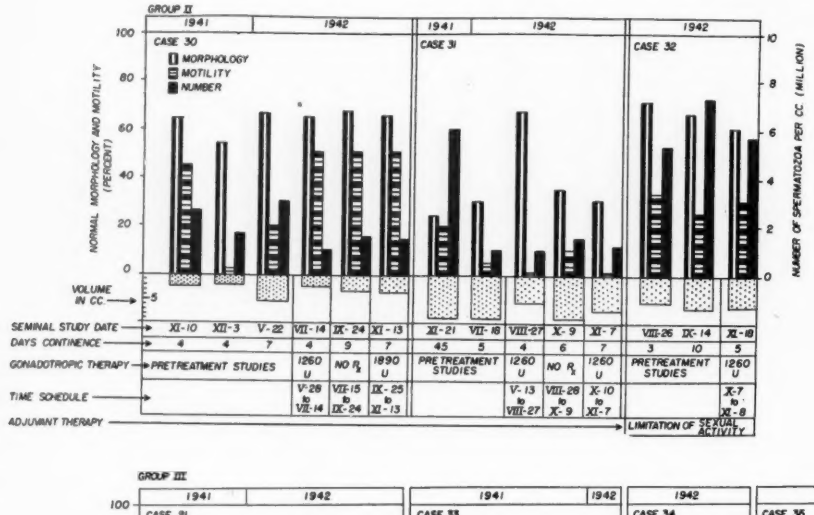
Further analyses of our data fail to demonstrate that therapy consistently improved any particular factor studied in the seminal examination: either volume, number of spermatozoa, morphology or immediate motility. Furthermore, there is no apparent correlation between the degree of seminal impairment and the effectiveness of therapy.

The statement made in our previous report (11) that none of the patients who received gonadotropic therapy permitted a definite diagnosis of hypogonadotropic pituitary failure applies equally to the patients included in this report. Until adequate clinical methods are devised for quantifying levels of pituitary function

and degrees of gonadal responsiveness, therapeutic testing of patients with gonadal deficiencies with gonadotropic extracts doubtlessly will continue to be considered expedient.

In view of a recent report of the occurrence of a severe anaphylactic reaction to CP+PS (12), comment on the tolerance of our patients to this preparation seems advisable. Despite the fact that no patient was treated who was not negative to skin tests with the preparation prior to each intended series of injections, one of our patients (not included in this series) had severe reactions which prevented continuation of therapy. Three hours after his first injection, there was a temperature of 38.8° C. and pain and swelling at the site of injection. One week later another injection was given and this was followed promptly by severe local and constitutional reactions—temperature of 40.0° C., chills and aching joints. Another patient had a severe local reaction to his first injection, which was given during a time when active immunizations preparatory to military service were being carried out. Later, when these were completed, he was able to proceed with CG+PS injections without any untoward reactions.

In conclusion, we are of the opinion that, had our analyses of data been confined solely to pre-



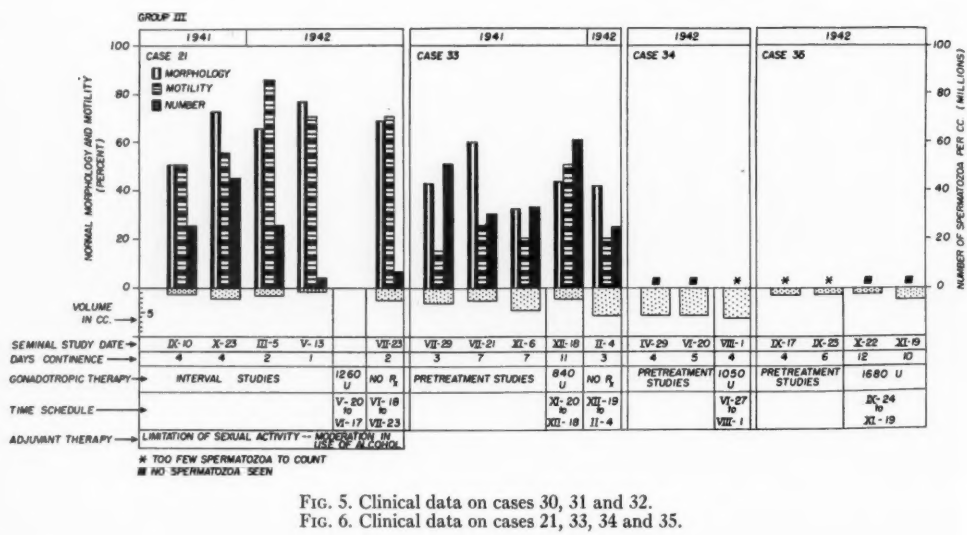


FIG. 5. Clinical data on cases 30, 31 and 32.
FIG. 6. Clinical data on cases 21, 33, 34 and 35.

treatment and treatment seminal values, we might have considered these data to justify the hope that an occasional patient might expect desirable effects on his fertility from this type of therapy. Our studies, however, of delayed post-treatment values, initiated as they were to explore the possibility that therapy with CG+ IS might exert delayed benefits, have nullified any real hopes for therapeutic salvage. These indicate not only that the few apparent improvements in seminal values which occur concurrently with treatment are evanescent and give way to values often lower than pretreatment ones when treatment has been discountinued but also that seminal values not improved during therapy often are depressed further in conjunction with this therapy. The cause of these apparent inverse responses has not been determined. Since these are not relatable to the higher dosage schedules employed or to the more protracted treatments given, it does not follow necessarily that these are due to antibody phenomena. This possibility, however, must be considered.

SUMMARY

Twenty male members of childless couples, with seminal inadequacy, whose ages (when first seen) ranged from 24 to 45 years and the duration of whose sterile matings ranged from ½ to 14 years, were investigated and treated with an extract containing chorionic gonadotropin and pituitary synergist.

Twelve of these patients presented no physical signs of andrologic disease; four had partial atrophy of one or both testes; and four gave evidence of chronic epididymitis and/or prostatitis. None presented symptoms or signs of pituitary disease or androgenic deficiency.

Therapeutic schedules embraced the daily intramuscular injection of 30 to 45 'synergy units' of the extract for four to twelve weeks, the average duration of a series of treatment being 5.7 weeks and the average series dosage being 1300 units. In all 27 series of injections were given.

Seminal values during therapy manifested no significant trend: in 8 of 18 patients these were elevated varying degrees while those of five patients were decreased. The fertility of one patient was judged to have been definitely enhanced in that his wife became pregnant.

Delayed post-treatment values, however, showed a definite trend (in 8 of 12 patients or 75%) toward levels lower than initial pre-treatment ones. Antibody phenomena were considered with regard to explaining these inverse responses.

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Breast Hypertrophy in the Male

Report of Two Cases of Pseudogynecomastia with Surgical Reconstruction

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IN THE LAST two years mobilization for military and industrial purposes has brought many young people into close proxmity in camps, barracks and factories where there is little personal privacy. As a result, certain physical abnormalities which are easily concealed in civilian life, can no longer be hidden. Among such malformations gynecomastia, is of relative frequent occurrence, often producing pronounced psychic depression.

Gynecomastia, a term applied to hypertrophy of the male breast, may present itself in two forms, true gynecomastia and pseudogynecomastia. The fomer is a tumor-like condition frequently due to proliferation of the ducts and periductal tissue. It is usually unilateral and of limited proportions and does not call for surgical intervention.

Many workers in this field have found true gynecomastia to be related to disturbances in the testes, pituitary gland and the adrenal cortex (1). It appears most frequently as a small, often painful, glandular swelling adherent to the nipple.

Prior to recent endocrinologic progress, the etiologic factors underlying this condition were more or less the subject of speculation. Recent work on the endocrines, however, shows that the female hormones are present in both males and females and that there may be an overbalance of female hormones in some males, and *vice versa* (2). True gynecomastia can be attributed to this hormonal imbalance and resulting sexual deficiencies.

Pseudogynecomastia is usually bilateral and manifests itself as an adiposis of the breast, which is soft, painless and may reach large proportions. Here to the normal glandular elements of the breast is added fatty hyperplasia. Hormonal therapy may have some influence on this adiposis, but it is rarely conquered thereby, and the patient suffers from extreme sensitiveness, often a pronounced psychic depression, because of the presence of mammary hypertrophy. This malformation can often be greatly improved by surgery.

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CASE HISTORIES

The following case histories are characteristic of the type of patient with pseudogynecomastia who is greatly benefited by surgery.

Case 1. (fig. 1). A male, age 30, was first seen in November, 1939. The patient had suffered from pronounced mental depression since the age of 15, avoiding the companionship of other youths and taking no part in sports of any kind. Even in the hottest summer weather he would insist on wearing a vest. His parents were completely ignorant of the factors underlying his abnormal mental state.

On physical examination no abnormalities were revealed except for local findings. At the age of 15 he had had a fibrocystic osteitis of the right arm, treated by roentgen-ray, which had left a conspicuous burn scar. The general appearance was that of a normally developed male, considerably overweight because of sedentary habits. His manner was shy and retiring, but he was able to conduct normal everyday business activities. The patient had a bilateral fatty hyperplasia of the breasts, which had the appearance of female breasts at puberty. They were slightly pendulous, soft, with a deep submammary fold. The areola was conspicuously large. No tumor-like masses could be palpated. There was no secretion from the ducts. The other sex characteristics, including the distribution of hair and the development of the sex organs were normal. During the previous 6 months he had been receiving treatment by a competent endocrinologist without result.

The patient admitted extreme sensitiveness about the mammary development which made him secretive about it, even with his closest relatives. Reconstructive surgery was advised and accepted without hesitation. The improvement following surgery was most gratifying. The entire mental attitude of the patient underwent a marked transformation for the better and he attained a complete mental and social rehabilitation.

The pathologist's report of the mammary tissue showed the hypertrophy to be due to adipose tissue; the breast stroma was normal with an average number of normal-appearing ducts and no acinar cells. The appearance of the specimen differed considerably from that of a true gynecomastia or fibroadenoma, in which there is proliferation or hypertrophy of the pericanalicular connective tissue with some hyperplasia of the duct epithelium.

Case 2, was a male, age 26, first examined in 1940. There was a slight overdevelopment of both breasts, which were of rather firm consistency. No tumor masses could be palpated and there was no secretion from the ducts. The breasts were moderately enlarged and about the size of normal mammae in a girl of 14. The areolae were enlarged. The patient appeared sexually normal.

In spite of the relatively limited malformation of the breasts, he exhibited great sensitiveness and reluctance to undress in the presence of others. He never took part in sports requiring removal of clothing and never went in swimming. The latter fact, he claimed, was the chief reason he sought medical advice. Inquiry into the familial history revealed pronounced breast hypertrophy in the mother and sister of the patient. For a number of months he had been undergoing regular endocrinologic treatment without improvement. Because of the moderate enlargement, surgery was not urged but was finally performed at the urgent request of the patient.

The microscopic examination of the removed breast tissue showed "fibrotic breast containing ductules with regular cuboidal epithelium, in the resting phase. Diagnosis: fibrotic breast tissue without significant changes in the epithelium." The mental improvement of the patient following surgery was gratifying.

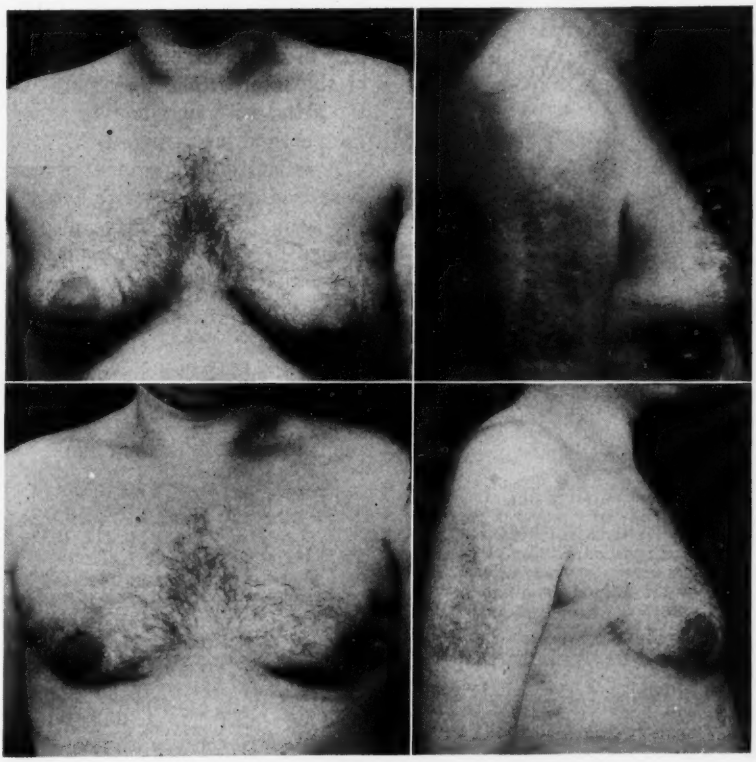

FIG. 1, *Case 1* (*above*). Pseudogynecomastia in a male, age 30. Surgical reconstruction consisted of a wedge-shaped excision from the posterior aspect of the gland. The incision was placed in the submammary fold. (*below*) Condition a few weeks after surgery. The incision placed in the submammary fold in time became indiscernible.

Surgical Procedure

The purpose of reconstructive surgery in these cases is to reduce the hypertrophy of the breast in the antero-posterior diameter without disturbing the nipple (fig. 2).

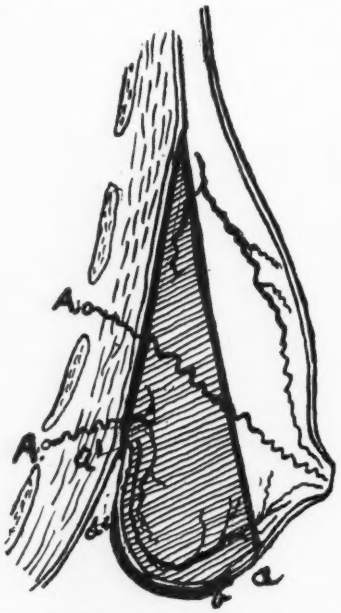

FIG. 2. Diagram illustrating the wedge-shaped excision from posterior aspect of mammary gland. a–a′, forms the base of the glandular wedge; b–b′, crescent-shaped excision of skin; A, branches of intercostal arteries which are easily retracted on the pectoral fascia from posterior surface of breast.

The incision is made in the submammary fold to conceal conspicuous scarring. The approach through the posterior aspect of the mammary gland permits avoidance of the two main vascular pedicles of the breast, the internal mammary artery and the lateral thoracic artery, on which the blood supply of the nipple and skin depends. This eliminates the problem of bleeding and allows easy separation of the mammary gland from the pectoral fascia. The only blood vessels encountered are the branches of the intercostals, which are retracted from the gland without difficulty as they run along the pectoral fascia (fig. 2, A).

A wedge-shaped segment of mammary tissue is excised along the entire height and width of the breast, leaving a section of the gland attached to the nipple. The amount of tissue to be removed depends on the extent of hypertrophy. Excess skin along the submammary fold is excised in a crescent shape (fig. 2, b–b′). Following careful hemostasis, the mammary gland is attached to the pectoral fascia. The incision is closed following some skin adjustment to equalize the skin flaps.

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Structure of the Human Anterior Pituitary Gland after Administration of Estrogenic Hormones

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IN THE PAST few years, there has been a large amount of experimental work on the effect of estrogenic and other steroid hormones on the anterior pituitary gland of several species of animals. The literature has been reviewed by Severinghaus (1, 2) and Zondek (3). This work has emphasized the markedly labile reactivity of the anterior pituitary, and has clarified some of its numerous inter-relationships with the other endocrine organs. It has also offered some clue to the genesis of 'adenomata' of the anterior lobe. However, with the exception of Zondek's (4) paper, there are no reports on similar experimental work in man.

This study was undertaken to determine the effects, if any, of different amounts of intramuscularly administered estrogens on the pituitary glands of men and women.

METHODS

Thirteen patients in advanced stages of chronic diseases were selected who had no obvious clinical endocrine disorder. These included cases with cardiac disease, pulmonary tuberculosis, malignant lymphomatosis and organic nervous disorders. Table 1 shows the age, sex, clinical diagnoses and the dosage schedule. Estrone[1] was used in doses of 20,000 I.U. (2 mg. of estrone) and estradiol benzoate[2] in doses of 1.66 mg. or 10,000 R.U. The injections were made at varying intervals, depending upon the condition of the patient. A complete autopsy was performed in most instances. In each case, the pituitary gland was weighed after fixation in Orth's fluid. The gland was sectioned sagittally at several levels. The sections were stained with hematoxylin-eosin and with Mallory's triple connective tissue stain preceded by hematoxylin. Cell counts of the anterior lobe were not made. Routine hematoxylin-eosin preparations were made of the other organs.

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[1] The estrone (Amniotin) was supplied by E. R. Squibb and Sons, New Brunswick, N. J.

[2] The estradiol benzoate (Progynon-B) was supplied by Schering Corp., Bloomfield, N. J.

FINDINGS

Case 1, male, aged 19 yr.; Hodgkin's disease. *Testes*. There was no spermatogenesis. Spermatogonia were present. Leydig cells appeared to be increased. *Pituitary*. The basophils were increased to about 20 per cent, the majority being ripe, with many bizarre forms. The transition basophils were increased in number, some showing hydropic and a few colloid change. The acidophils were normal in appearance. There was some hyperplasia but its relation to the administered estrogen was in doubt due to the testicular changes.

Case 2, male, age 21, pulmonary tuberculosis. *Testes*. There was some decrease in spermatogenesis. A few spermatids and rare spermatozoa were present. The Leydig cells seemed to be slightly increased. *Pituitary*. There was an average number of basophils but the nuclei were enlarged and vesicular. The number of transition forms were increased, with a few at the hydropic stage. The acidophils were increased in number, their nuclei enlarged and vesicular. There was a moderate degree of granule loss up to the hydropic stage. There was a minute nodule of transition acidophils (fig. 3). The capillaries were compressed. There was hyperplasia involving largely the acidophils.

Case 3, male, age 22, pulmonary tuberculosis. *Testes*. There was active spermatogenesis. The Leydig cells were decreased. *Liver*. There was slight amyloidosis. *Pituitary*. The basophils were increased to about 30 per cent and there were large numbers of swollen, watery transition basophils with swollen nuclei (fig. 1). Basophils of the castration cell type with pyknotic nuclei were also present. The acidophils were increased in number with marked pleomorphism, granule loss and nuclear hypertrophy. Many binucleated chromophils were present; the capillaries were compressed. There was a marked hyperplasia, involving acidophils and basophils, largely the latter.

Case 4, male, age 23, pulmonary tuberculosis. *Testes.* Spermatogenesis was arrested at spermatogonia stage and the Leydig cells appeared to be increased. *Pituitary.* The basophils were increased to about 20 per cent, the majority being ripe with slight increase in transition forms. The acidophils were increased, with only a few atypical forms. A minute nodule of transition basophils was present in the lateral portion of the anterior lobe. There was an increase in the number of ripe chromophils.

Case 5, male, age 23, Hodgkin's disease. *Testes.* Spermatogenesis was arrested at spermatocyte stage. Leydig cells were present in average numbers. *Pituitary.* The basophils were present in average numbers, the majority of which were ripe. A few transition forms were observed. The acidophils were increased in number, the majority of which were ripe, but the transition forms were increased with the appearance of growth in places. There was one large sheet of hydropic transition acidophils. A moderate number of chromophils of the castration cell form of both types were present. A mild hyperplasia existed chiefly involving the acidophils.

Case 6, male, age 24, pulmonary tuberculosis. *Testes.* Spermatogenesis arrested at spermatocyte stage, with a few spermatids present. The Leydig cells appeared to be average in number. *Pituitary.* There was a slight increase in the basophils; the transition forms were increased in number with few at the hydropic stage. The acidophils were increased, as were the transition forms with several minute areas of simple hyperplasia near the pars intermedia. There was a microscopic nodule of polygonal vacuolated transition basophils and a minute area containing atypical, transition acidophils appearing to be localized simple hyperplasia. There was a small focus of simple hyperplasia consisting of small transition basophils. There was a generalized mild hyperplasia with several localized foci.

TABLE 1. STRUCTURE OF HUMAN ANTERIOR PITUITARY GLAND FOLLOWING ESTROGEN ADMINISTRATION

Case No.	Age	Sex	Diagnosis	Total Dose of Estrogen[1]	Period of Treatment	Interval after Last Dose	Weight of Pituitary	Structure of Anterior Pituitary
	yr.				*days*	*days*	*mg.*	
1	19	M	Hodgkin's disease	260,000 I.U. (26 mg. estrone)	25	3	615[2]	Appeared normal
2	21	M	Pulmonary tuberculosis	120,000 I.U. (12 mg. estrone)	27	4	475[2]	Mild hyperplasia
3	22	M	Pulmonary tuberculosis	240,000 I.U. (24 mg. estrone)	68	34	450[2]	Marked hyperplasia
4	23	M	Pulmonary tuberculosis	60,000 I.U. (6 mg. estrone)	8	83	490[2]	Appeared normal
5	23	M	Hodgkin's disease	100,000 I.U. (10 mg. estrone)	9	2	320[2]	Mild hyperplasia
6	24	M	Pulmonary tuberculosis	180,000 I.U. (18 mg. estrone)	12	2	510[2]	Mild hyperplasia
7	34	M	Lymphosarcoma	20,000 I.U. (2 mg. estrone)	1		450	Appeared normal
8	60	M	Multiple sclerosis	6.6 mg. estrad. benz. (40,000 R.U.)	9	3	575	Marked hyperplasia
9	65	M	Amyotrophic lateral sclerosis	43.8 mg. estrad. benz. (264,000 R.U.)	294	1	410	Marked hyperplasia
10	25	F	Rheumatic heart dis.	200,000 I.U. (20 mg. estrone)	31		430[2]	Mild hyperplasia
11	27	F	Rheumatic heart dis.	220,000 I.U. (22 mg. estrone)	29	3	685	Appeared normal
12	32	F	Pulmonary tuberculosis	40,000 I.U. (4 mg. estrone)	4	3	635[2]	Appeared normal
13	32	F	Pulmonary tuberculosis	11.6 mg. estrad. benz. (70,000 R.U.)	9	1	720	Marked hyperplasia

[1] 10,000 I.U. of estrone (Amniotin) = 1 mg. of estrone; 1.667 mg. of estradiol benzoate (Progynon-B) = 10,000 R.U. (Allen-Doisy). The estrone unit is not the same as the estradiol benzoate unit. One gm. of estrone = 10,000 I.U. One gm. of estradiol benzoate = 10,000 I.B.U. On biologic test, estradiol benzoate is 6 times as effective as estrone, mg. for mg.

[2] Denotes slight damage to posterior lobe in removal. Hence the true weight is slightly greater.

Case 7, male, age 34, lymphosarcoma. *Testes.* Spermatogenesis was arrested at the spermatogonia stage. The Leydig cells seemed to be slightly increased. *Pituitary.* The basophils were increased to about 25 per cent and there were small adenomatoid nodules of ripe cells, many of which were bizarre in form. The acidophils showed a moderate degree of pleomorphism. Numerous hydropic, degranulated cells with large vesicular nuclei were seen; these probably were of acidophilic and basophilic origin. Some hyperplasia was noted.

Case 8, male, age 60, multiple sclerosis. *Testes.* There was a very slight decrease in spermatogenesis. The Leydig cells present were average in number. *Pituitary.* The basophils, average in number, had en-

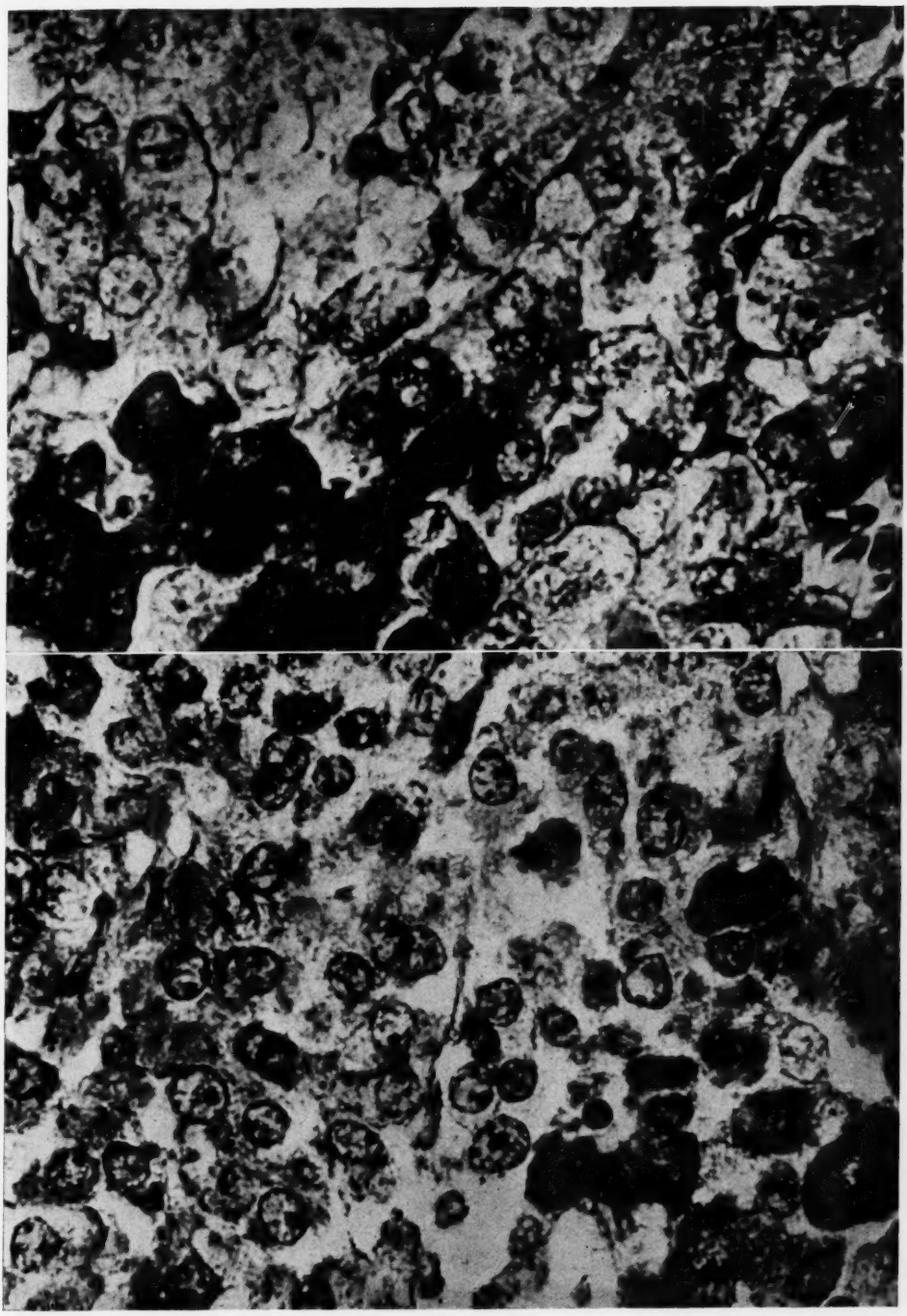

FIG. 1 (*upper*). Anterior region of anterior lobe, *case 3*. The ripe basophils appear dark. The transition basophils are hydropic and swollen and closely approximated. Nuclei are enlarged and vesicular. No acidophils shown in microphotograph. ×650.

FIG. 2 (*lower*). Posterior region of anterior lobe, *case 13*. The ripe acidophils appear dark. Note the syncytial appearance of the transition acidophils, with large vesicular nuclei, prominent nucleoli and watery cytoplasm containing lightly staining granules. No basophils shown in microphotograph. ×650.

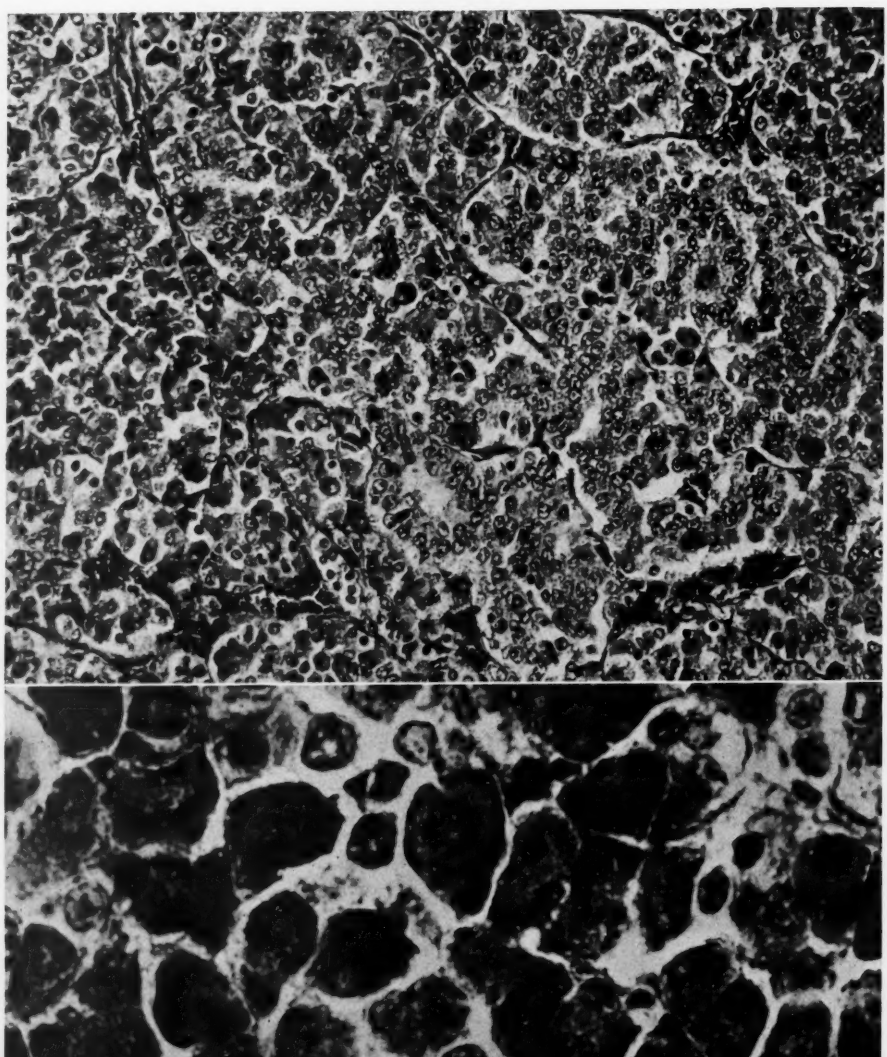

FIG. 3 (*upper*). Posterior region of anterior lobe, *case 2*. Localized area of hyperplasia of transition acidophils. Cells arranged in anastomosing cords. ×160.

FIG. 4 (*lower*). Anterior lobe, *case 10*. Ripe acidophils. Note solid chromatin of nuclei of normal size. Granules are large and stain deeply. Compare with degranulated acidophils in figure 2. ×650.

larged vesicular nuclei. The number of transition forms was increased and colloid changes were observed in a small proportion; one mitotic figure occurred. There were several minute areas of simple hyperplasia of ripe and transition basophils. The acidophils were increased in number and had enlarged and vesicular nuclei; the granule loss was moderate and there were numerous hydropic cells. Numerous small areas of simple hyperplasia of ripe or degranulated acidophils were observed. There was compression of the capillary bed and marked hyperplasia chiefly involving the acidophils.

Case 9, male, age 65, amyotrophic lateral sclerosis. The brain and hypophysis only were examined. *Pituitary*. There was a slight increase in the number of basophils and of the transition forms up to the hydropic stage. The nuclei of the transition cells were either large and vesicular or small and dark (castration cell type). There were several foci of syncytial transition basophils. Many of the basophils invading the posterior lobe showed granule dispersion with hydrops of the cytoplasm. The acidophils and transition forms were increased. There was an area of simple localized hyperplasia of transition acidophils adjacent to the pars intermedia. A small nodule of hydropic, transition cells, probably acidophilic in origin, was observed at the anterior pole. The capillary bed was compressed. A marked general hyperplasia involving anterior lobe cells and posterior lobe basophils was apparent with two localized areas of hyperplasia of acidophils.

Case 10, female age 25, rheumatic heart disease. *Ovaries and uterus*. No abnormalities. Endometrium in interval stage. *Pituitary*. The basophils were average in number with many atypical ripe cells. A few showed granule dispersion, some approaching the colloid type. There was one minute nodule composed of atypical transition basophils. The acidophils were increased in number, the majority being ripe (fig. 4). There were many transition forms including a large sheet of hydropic transition acidophils in the region of the pars intermedia. There was a minute nodule of atypical transition acidophils adjacent to Rathke's cleft. Scattered castration cells with dark nuclei were observed. There was a mild hyperplasia chiefly affecting the acidophils and several minute foci of localized simple hyperplasia of acidophils and basophils.

Case 11, female, age 27, rheumatic heart disease. *Ovaries and uterus*. No abnormalities. Endometrium at interval stage. *Pituitary*. The basophils were average in number and of normal morphology. The acidophils were increased in number, but were of normal morphology. Four areas of nodular hyperplasia were present: 1), 2 mm. in width composed of cells, chromophobes, acidophils and basophils; 2), ½ mm. in width containing transition and ripe basophils, 3), ½ mm. in width consisting of transition and ripe acidophils and 4), a small nodule of transition and ripe basophils. There was no diffuse hyperplasia.

Case 12, female, age 32, pulmonary tuberculosis. *Ovaries and uterus*. No abnormalities were observed. *Thyroid*. There were areas of atrophy and hyperplasia. *Liver*. There was evidence of very slight amyloidosis. *Pituitary*. The basophils were average in number, the majority of which were ripe. A few transition forms were observed. The acidophils were increased in number and the majority were ripe and had large vesicular nuclei. More than half of these had large nuclei and scanty, granular cytoplasm. There was only slight granule loss from the many huge, ripe acidophils, some with 2 or 3 nuclei. There was a mild hyperplasia affecting the acidophils.

Case 13, female, age 32, pulmonary tuberculosis. Only pituitary examined. The basophils were increased to about 15 per cent. Small nodules of adenomatoid hyperplasia occurred. The majority of the basophils were ripe, but there were numerous transition forms, some of which were at the hydropic stage. There was a marked increase in the number of acidophils with enlarged nuclei which were either vesicular or hyperchromatic. There was a marked granule loss (fig. 2). Several small areas of simple localized hyperplasia of atypical transition acidophils occurred, one appearing almost neoplastic. In the anterior region there was a microscopic nodule of atypical transition acidophils. The capillary bed was compressed. Hyperplasia was marked and largely involved the acidophils; minute areas of localized hyperplasia were observed.

GENERAL DISCUSSION

The anterior pituitary can respond to a given agent by hyperplasia of a normal gland, or involution of a hyperplastic one.

With hyperplasia, a new formation of chromophils from chromophobes is observed. The nuclei enlarge, with or without changes in the chromatin content, and they may also divide amitotically to form binucleated or multinucleated cells. Pyknosis may occur as a manifestation of cell exhaustion. The cytoplasm may show granule loss or dispersion, with either a watery, vacuolated or colloid ground substance remaining. Changes in cell shape and thinning of the capillary bed are due to altered pressure relationships, resulting from cellular hyperplasia and hypertrophy. Localized areas of hyperplasia may occur, and these may be well circumscribed, and take the form of the so-called adenoma. This type of hyperplasia is found in the human anterior pituitary in pregnancy, and in the experimental animal after thyroidectomy or estrogen administraion. I have observed the same type of response in several eunuchoid male individuals. A complex morphologic picture can be produced in the an-

terior pituitary when, as frequently occurs, more than one agent acts upon it. The confusion in the literature regarding pituitary morphology in different conditions can thus be readily understood.

Although changes in the cell proportions in the direction of increased numbers of ripe acidophils and basophils are observed in a large variety of clinical conditions, a marked loss of granules is seen only when there is a definite alteration in the hormonal balance. A disturbance of the androgen-estrogen ratio can account for the degranulation of the chromophile cells in pregnancy, in disturbances of gonadal function, and in the hormone-injected animal. The changes in the basophil cells in Cushing's syndrome (5) are probably secondary to a more complex disturbance in the metabolism of the steroid hormones.

It is of interest to note that in the 3 cases receiving the benzoate ester there was a marked hyperplasia of the anterior pituitary, whereas only one of the estrone-injected cases revealed extensive changes. However, the number of cases is too small to justify conclusions regarding the relative potency of the two estrogens. In addition to the rate of absorption and duration of action of the two preparations, one must consider the production by the organism of androgens or other steroids to counterbalance the excess of estrogen. Also, the rate of inactivation of the estrogen by the liver must play an important rôle. Impaired liver function would thus enhance the effect of any given dose of estrogen. There probably are other factors which influence the individual response.

This series of cases is too small to evaluate the time factor in relation to the degree of cellular reaction. It is of interest to note that *case 13*, the pituitary of which showed the most pronounced acidophil changes, received only 11.6 mg. of estradiol benzoate in 9 days, whereas the pituitary of *case 9*, which was treated with 43.8 mg. of the same estrogen over a period of 42 weeks, revealed a less marked change in the acidophils. The influence of age, sex and underlying disease also cannot be judged because of insufficient data.

The 4 cases that were classified as marked hyperplasia showed individual features that deserve special comment. *Case 3* showed the most pronounced changes in the basophil cells, not only in this group of cases, but with one exception (13) in the several hundreds of pituitary glands that I have examined. The basophil cells were increased to about 30 per cent (normal 5–10 per cent), but only half of them contained ripe granules. The degranulated basophils were large and polygonal, with large vesicular nuclei and a watery, finely granular, faintly basophilic cytoplasm (fig. 1). Castration cells with small dark nuclei also were numerous. The acidophils in this case also exhibited marked pleomorphism and granule loss. These changes are remarkable and 34 days had elapsed after the last dose of estrogen. Slight amyloidosis of the liver was present in this individual, and this may have interfered with the inactivation of the estrogen, resulting in an intensification of its effect. There were no apparent clinical or morphologic changes in the other endocrine organs that might have accounted for these alterations in the anterior pituitary.

Case 13 revealed the most extensive loss of acidophil granules. The remaining granular acidophils stood out prominently as small islands among sheets of transition cells (fig. 2). Some of these degranulating acidophils had a very bizarre morphology, and under high magnification appeared almost neoplastic. This patient had received in a period of 9 days 11.6 mg. of estradiol benzoate. Although a complete autopsy was not performed, it seems reasonably certain that these cytologic changes were related to the administered estrogen, since I have never seen as marked acidophil degranulation in any other pituitary.

Case 8 is of interest because of the alterations in the basophil cells. Granule dispersion was prominent and cells approaching the colloid type were fairly numerous. One basophil cell was observed in the prophase stage of mitotic division. Although mitosis is not rare in the anterior pituitaries of animals receiving estrogens, or after thyroidectomy, I have never before observed it in a human gland.

Finally, *case 9* deserves attention because of the prolonged administration (10 months) of estradiol benzoate to a man. There were no morphologic changes in the other organs. The anterior pituitary revealed fairly extensive granule loss and a minute, localized nodule of

watery, degranulated acidophils at the anterior pole.

Investigation of a much larger series of patients under a greater variety of experimental conditions would be necessary to determine the minimal dose of estrogen necessary to produce morphologic changes in the human anterior pituitary. Relatively huge doses of estrogen over a relatively long period of time are necessary to produce structural changes in the animal pituitary. On the basis of available data, it is likely that the amounts of estrogen employed in the present studies were sufficient to produce changes in the hormonal balance. Corner (14) estimated, on the basis of comparison with the Macacus rhesus monkey that the human adult female secretes about 3000 I.U. (300 gamma) of estrone daily. Even if this estimate should be too low, the androgen-estrogen ratio must have been altered in all 4 female patients by the dosage of estrogen used. It is obvious that the change in the hormonal balance must have been even greater in the case of the males in whom the secretion of estrogen is normally at a very low level.

The problem arises of whether the structural alterations produced in the anterior pituitary by estrogens represent a stimulation or a depression of function. Zondek (3) stated that estrone could either activate or depress the function of the anterior lobe, depending upon the amount of hormone administered and the duration of its action. Small doses stimulated, while large doses depressed function. If the administration of estrogen in animals was prolonged, the gonadotropic function of the pituitary was first depressed, and later the elaboration of the growth factor was decreased. However, large amounts of hormone were necessary to inhibit the growth of young rats. For example, 2900 I.U. of estrone or estradiol benzoate in oil given subcutaneously over a period of 4 months to rats weighing 25 gm. had no effect on body growth. An equivalent dosage in a young child would be about 3,000,000 I.U. of the hormone over a proportionately longer period. However, 12,000 I.U. of aqueous estrone within 5.5 weeks was accompanied by a reduction of 9.6 per cent of body weight. This would be approximately equivalent to 12,000,000 I.U. of estrone to a young child.

It is of interest to note (3) that the hypophyses of eunuchoid dwarf rats contained no less gonadotropic factor than those of control animals. Zondek thus concluded that there had been interference only with the delivery into the blood stream of the gonadotropic factor. However, Severinghaus (1) stated that there was a decrease in the sex stimulating potency of pituitary glands showing basophilic degranulation after pregnancy urine extract injections. It is difficult to reconcile these two views. One cannot rely upon implantation experiments to determine the functional status of the anterior pituitary, for only hormone storage is thus measured. Assay of a hyperactive or an exhausted gland would both show a low hormone content, while a resting gland would contain a high hormone level. There are no accurate methods of assay for the several hormones of the anterior pituitary, all of the biologic tests for tropic factors being only rough approximations. Furthermore, considerable alteration of function can occur without specific morphologic change and *vice versa*. A similar situation obtains in the case of the thyroid gland. The hyperplasia of endemic goiter and that of Graves' disease may be indistinguishable. Hence, one must be very cautious in attempting to estimate the functional status of the anterior pituitary by even the most refined cytologic methods.

In certain cases, however, one may be able to judge anterior pituitary function by combined clinical and anatomic studies. For example, it is accepted that acromegaly is caused by a hyperfunction of the acidophil cells. One may then reason that the hyperplasia and degranulation of the acidophils which occurs in the anterior pituitary during pregnancy represents hypersecretion, since acromegaloid features are not uncommon during the gravid state.

Clinical experimentation may offer some clue as to the amount of estrogen necessary to depress the gonadotropic function of the anterior pituitary. According to Zondek (3), 70,000 to 600,000 I.U. of estradiol benzoate can bring about inhibition of menstruation for from 7–70 days. There is a considerable degree of individual variation in the dosage of estrogen necessary to produce this effect.

At this point, it would be pertinent to review

Zondek's case of massive estrogen administration to a young woman (4). This was an instance of post-operative metastatic mammary carcinoma in a 26-year-old woman. She received 0.6 gm. (6,000,000 I.U.) of estradiol benzoate over a period of 60 days. The estrogen was given on the 14th day of the cycle and the expected menses was delayed 25 days and was scanty (one day). The next bleeding occurred 32 days later, and lasted only several hours. Death occurred on that day. At autopsy, the pituitary gland weighed 710 mg. and showed a large, circumscribed area of acidophil hyperplasia in theupper posterior zone and occupying half of the entire anterior lobe. The endometrium showed glandular cystic hyperplasia, hyperemia and hemorrhage. The cervix revealed a papillary erosion. The ovaries had no primary or ripening follicles and no corpus luteum. The other organs showed no changes. Zondek concluded that the ovarian changes were due to depression of the gonadotropic function by the estrogen. The changes in the cervix and endometrium were local effects due to the huge doses of estrogen. According to Zondek, it is thus possible to induce functional castration by large doses of estrogenic hormone.

SUMMARY

Nine male and 4 female patients were treated with estrogenic hormone over varying periods of time and the pituitary glands were examined cytologically. All 3 of the cases receiving the estradiol benzoate and one receiving estrone showed marked hyperplasia of the chromophil cells. The cytologic structure resembled that produced in animals by estrogen injection. No changes were observed in the other organs examined.

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EDITORIAL

DOES ANDROGEN THERAPY ENDANGER THE TESTIS?

According to existing evidence, administration of androgens can either depress or enhance spermatogenesis. What conditions determine the results are not yet well understood.

Important evidence indicating testis damage by androgens has been presented by Moore and Price.[1] They showed that when 0.1 mg. of testosterone propionate was administered daily to young rats for a period of 3 weeks, the resultant testis weights were 20 to 25 per cent of those of the littermate controls and that the germinal epithelium was markedly injured. In the immature rats in Moore's experiments the smallest dose of androgens produced the greatest testis damage while the largest doses produced the least damage. In the adult rat, testicular hormone has never been shown to damage the testes. A warning that deleterious effects to the testes might follow the use of androgens in man seemed timely, especially when various workers[2,3] observed clinically that injections of testosterone propionate in doses approximating 75 mg. per week over a period of two or three months depressed the sperm count, and at times to very low levels. However when semen examinations were repeated following cessation of therapy, the sperm counts rose again to their original height or exceeded it. Similar results were seen following the oral administration of methyl testosterone. The effects of small doses of androgens in man is still indeterminate.

Walsh[4] in 1934 showed that when large amounts of androgens were given to hypophysectomized rats not only did the usual rapid testicular degeneration fail to occur but also spermatogenesis was maintained. Nelson[5] corroborated and extended these findings. Later he showed that testicular regeneration could be evoked by injections of androgens plus adrenal cortical hormone even weeks after hypophysectomy without treatment. Other experimental data showing that androgens support spermatogenesis include the findings that hypophysectomized ground squirrels show testicular activity after treatment with androsterone and testosterone.[6] If the ground squirrel in a sexually immature state is treated with androsterone or testis extracts, sperm will be produced earlier than normal.[7]

Cuyler[8] observed that in certain birds which appeared to be capons the comb growth behaved in an unusual way following injections of androgenic urinary extracts. After showing marked growth the comb regressed very little or none at all between injections, so that with each successiv injections the comb more closely similated that of a normal cock until a fully normal appearance was attained. Such birds at autopsy always showed testis tissue and frequently had an hypertrophied mass of tissue much larger than the original testis. Such apparent testis stimulation may not be specific, however, since testicular degeneration consequent to hypophysectomy may be prevented by progesterone[9] and by yeast.[10] It is interesting in this respect to note that in rams sperm production may be stimulated by stilbesterol also.[11]

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In rats, very low and very high doses of androgens may stimulate spermatogenesis while intermediate doses have depressing effects. Rubinstein[12] showed that when immature rats were given doses of testosterone propionate of 5.0 micrograms daily, the testis weights increased, whereas doses of 50.0 micrograms caused a decrease. Using higher doses, Shay[13] found that 3.0 mg. per week inhibited sperm maturation in rats, while 30.0 mg. per week was followed by increased weight of the testes and stimulation of sperm production.

In man the chief indication for the use of androgens is not in the treatment of sterility. The bulk of evidence indicates a depressing effect of the materials upon spermatogenesis. Clinical evidence that small doses of androgen may be useful in human sterility is too meager to warrant the general use of these agents for this purpose. For the present, then, the most practical clinical use of androgens is as replacement therapy where clear evidence of androgen deficiency exists.

In boys in whom adolescent changes are delayed, gonadotropins are usually indicated. If these substances fail to stimulate the testes to the production of normal quantities of androgens, then the administration of androgens themselves may be warranted. Inhibition of sperm production should be considered as a possible result of such treatment. In men repeated sperm counts serve as an index of fertility. In boys, however, such a test is not obtainable. In order to maintain any potential fertility and to avoid reducing chances for fertility in the future, courses of treatment should be interrupted by periods of rest.

Clinicians should remember that the problem is still in the stage of clinical experimentation.

E.P.McC.

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LETTERS TO THE EDITOR

NUTRITIONAL DEFICIENCY AND MATERNAL BEHAVIOR

TO THE EDITOR:

In a letter to the Editor in the March issue of this Journal, Dr. David M. Levy commented on studies he has made on mothers of children under treatment for behavior problems. He found that there is a relationship "between the habitual number of days of menstrual flow and the strength of the maternal feeling" and that "a significantly higher proportion of strong maternal impulses appeared in the woman having a flow of 6 to 8 days than in the group flowing from 2 to 4 days."

Observations, previously made in animals, that the liver loses its ability to inactivate estrogen in vitamin B-complex deficiency,[1,2,3] led us to investigate the relation of nutritional deficiency to the occurrence of clinical syndromes associated with an excess of estrogen. In a study already reported,[4] and in others now in progress we have observed that women with prolonged menstrual periods usually suffer also from premenstrual tension and that deficiency of the vitamin-B complex is concerned in the etiology of both syndromes. The excessive irritability in these women often persists through the entire month, becoming more severe as the estrogen level rises further in the latter part of the intermenstruum. This would seem to be an important factor in inducing behavior problems in the children. Several patients whose chief complaint was menorrhagia, spontaneously expressed concern because they had been becoming increasingly short-tempered with their children. This was accompanied by an attitude of obvious over-solicitude.

Treatment of the nutritional deficiency in these patients with vitamin-B complex in adequate dosage orally, or orally and parenterally, led not only to diminution in the amount and duration of the menstrual flow but also to prompt disappearance of the excessive irritability.

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Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: DANIEL A. MCGINTY. *Collaborators:* ISRAEL BRAM, JOHN C. DONALDSON, J. W. EVERETT, MURRAY B. GORDON, R. B. GREENBLATT, E. C. HAMBLEN, HANS O. HATERIUS, CHARLES W. HOOKER, R. G. HOSKINS, J. E. HOWARD, J. T. LEWIS, T. H. MCGAVACK, A. E. MEYER, MARY L. MILLER, C. C. PFEIFFER, DORIS PHELPS, J. P. PRATT, E. C. REIFENSTEIN, JR., BORIS B. RUBENSTEIN, PATRICIA H. SMITH, RUTH ST. JOHN, CHARLES W. TURNER, EMMERICH VON HAAM, HAROLD WOOSTER.

BOOK REVIEW

LEMOS TORRES, ULISSES.
Hyperthyroidism and its treatment. São Paulo, 1942, 342 pp.

The author distinguishes six different types or grades of hyperthyroidism: (1) hyperthyroidal constitution; (2) Graves' disease, with 5 subgroups; (3) hyperthyroidism caused by general hormonic disequilibrium, especially of pituitary origin; (4) by adenoma; (5) by inflammation; (6) by neoplasm. Various types are illustrated by case reports (15 in all) which excel in their completeness of personal histories and clinical and laboratory data and which are supplemented by photomicrographs showing the structure of the removed thyroid. Many of the proposed theories, e.g., iodine-Basedow as a consequence of iodine treatment of a non-toxic adenoma, are culled from debatable literature. In his introductory chapters on the anatomy and physiology of the thyroid and also in most of the rest of the accompanying text, the author tries to account for as much of the abundant literature as his limited space permits. The reader is impressed with the variegated and often contradictory theories advanced on the normal and pathological physiology of the thyroid.—*A.E.M.*

ADRENALS

HASELTINE, S. L.
Later report on suprarenal gland in the treatment of glaucoma, progressive myopia, and some allergic conditions. *J. Am. Inst. Homeotherapy* 36: 85. 1943.

Oral administration of 8 to 15 mg. of adrenal gland, 1 to 3 times a day, is of value in these conditions and in hay fever, asthma, vernal catarrh and eczema. Eight case reports are presented.—*Courtesy Biol. Absts.*

HENI, F.
The sublingual administration of desoxycorticosterone in the treatment of Addison's disease. *Deutsche med. Wchnschr.* 68: 162. 1942.

Three cases of successful use of the acetate, DCA, by sublingual administration in Addison's disease are reported. Absorption is sufficient but the dose must be about ⅓ higher than in intramuscular administration. Overdosage may result from continued administration of 10 mg. or more. Blood studies are included.—*Courtesy Biol. Absts.*

HENI, F.
Problems in the utilization of desoxycorticosterone and similar substances in actual cortical insufficiency. *Deutsche med. Wchnschr.* 68: 318. 1942.

Desoxycorticosterone acetate affects salt and water metabolism more strongly than the carbohydrate metabolism, in Addison's disease. The effect on K metabolism is less than that on Na, and it is suggested that carbohydrate metabolism is influenced by potassium concentration. DCA did not completely restore health in 4 patients with severe Addison's disease, although it is highly effective in mild or moderate cases. Progesterone has a beneficial effect on carbohydrate metabolism in severe Addison's disease; testosterone and estrone increase general tone only in mild cases. These related sterones do not act on salt metabolism but increase the glycogen reserve of muscle. Progesterone may be used in certain severe cases of Addison's disease in which DCA produces disturbances of water and salt metabolism. The effect of the various agents on glucose tolerance is compared.—*Courtesy Biol. Absts.*

KOSTER, H. AND L. P. KASMAN.
Effect of desoxycorticosterone acetate in postoperative shock. *Arch. Surg.* 45: 272. 1942.

200 patients operated on for conditions such that shock might reasonably be expected to develop during or after the operation were studied. 100 alternately chosen patients were treated with desoxycorticosterone acetate, one to two days preoperative and ten to twelve days postoperative. The other 100 patients were given parenteral NaCl solution. Mortality rate in the treated and control groups was used as the criterion of effectiveness of therapy. There was no evidence that desoxycorticosterone therapy prevented or influenced the shock state favorably.—*D.A.M.*

SARASON, E. L.
Morphologic changes in the rat's adrenal under various experimental conditions. *Arch. Path.* 35: 373. 1943.

Changes in weight of adrenals relative to body weight and lipid deposition, observed histologically, were studied in rats subjected to (1) desoxycorticosterone acetate, (2) hypophysectomy, (3) castration, (4) inanition, (5) high protein and (6) high potassium diets and (7) stilbestrol. Administration of 2 mg. of desoxycorticosterone acetate per day for one month resulted in atrophy of the adrenal in the male but not in the female. In both, the zona glomerulosa was shrunken and depleted of lipid. In the atrophy following hypophysectomy the zona fasciculata was shrunken and the zona glomerulosa became slightly hyperplastic. Administration of desoxycorticosterone acetate to these rats resulted in further atrophy of the adrenal associated with shrinkage and depletion of lipid of the zona glomerulosa. This indicates that adrenal atrophy following desoxycorticosterone acetate is not mediated through the pituitary. Acute inanition in the female resulted in moderate adrenal hypertrophy accompanied, in about half the animals, by depletion of cortical lipids. Adrenals of rats fed for a month on a diet containing 45–50% protein and of rats receiving, after a 24 hour fast, an injection of 5 mg. of stilbestrol per 100 g of body weight, showed adrenal hypertrophy and some degree of lipid depletion.—*M.L.M.*

SCUDDER, J. AND R. H. E. ELLIOTT.
Controlled fluid therapy in burns. *J. South. M. and Surg.* 104: 651. 1942.

Case report illustrating severe hemoconcentration, electrolyte changes, acidosis, hypoproteinemia, sodium loss and hyperpotassemia which occur early in the burn syndrome; and the hyperbilirubinemia, hypocholestremia and anemia seen later. Therapy included serum, salt, adrenal cortical extract, glucose, oxygen, plasma, blood transfusions, and a high protein and high vitamin diet. The successful use of cortical extract is emphasized.—*D.A.M.*

TAYLOR, C. E., AND B. H. KEAN.
Waterhouse-Friderichsen syndrome on Isthmus of Panama. *Am. J. Dis. Child.* 65: 426. 1943.

Two cases in mestizo infants are reported. The first, a girl aged 25 days, is the youngest except one in the literature. At postmortem she showed extensive bilateral adrenal hemorrhages, a congenital polycystic kidney (left), moderate congestion of the lungs, moderate congestion of the leptomeninges, severe congestion of the mucosa of the larynx and trachea, small bilateral subconjunctival hemorrhages, small cysts of the base of the tongue, cyanotic mottling of the skin, a relatively large normal thymus, and a total absence of lesions in the periadrenal tissue. The second, a girl of 2 months, was found at autopsy to have hemorrhage of the left adrenal, bilateral suppurative otitis media, severe tubular degeneration of the kidneys, malnutrition, hypoplasia of the thymus, and no hemorrhage in the periadrenal tissue. In both cases the hemorrhage had destroyed the medulla and a large part of the cortex of the glands. The meningococcus was not demonstrated in either case. Both patients had an acute clinical course with high fever, gastro-intestinal and respiratory symptoms and collapse. These are the first cases to be reported from Central America and bring the total of published cases to 107.—*E.C.R., Jr.*

ENDOCRINE GENERAL

BICKERS, W.
Primary dysmenorrhea. *South. M. J.* 36: 192. 1943.

The normal and dysmenorrheic patient have been compared according to general body structure, psychic factors, age, family history, menstrual regularity, endocrine status as shown by the consistent presence of a corpus luteum, endocrine status, anatomy of the uterus, histology of the uterus and myometrial physiology. The only difference found between the two groups was the constant alteration in myometrial physiology in the dysmenorrheic uterus. A condom ballon was inserted into the uterus, and connected through a catheter to a kymograph. Tracings of uterine

contracts during menstruation were taken on 17 dysmenorrheic patients and a group of normal control. Myometrial spasm was demonstrated in the dysmenorrheic group. This spasm could not be abolished by atropine, ephedrine, epinephrine, calcium gluconate, and benzedrine sulfate. A new spasmolytic, non-narcotic, pavarine-like drug, pavatrine, abolished myometrial spasm and inhibited uterine contractions in about one third of the dysmenorrheic uteri. Estrogens, progesterone and testosterone did not alter the pattern of human motility in the human uterus. The author recommends a flexible stem pessary, inserted on the last day of menstruation, which will act as a foreign body to stimulate a congenitally defective myometrium to expulsive contractions, with improvement in the myometrial physiology. In a majority of the patients with dysmenorrhea the uterine spasm will be abolished after the pessary has been in place for 6 weeks.—*H.W.*

Bronstein, I. P., L. J. Halpern and A. W. Brown.
Obesity in children. *J. Pediat.* 21: 485. 1942.

Of a large group of children referred with tentative diagnoses of Fröhlich's syndrome, studies of 46 children, ranging from 4 to 15 years, comprise this report. History and physical and laboratory examinations of each child on admission and at regular intervals thereafter, over an observation period ranging from 6 months to 6 years, were conducted to establish any evidence of glandular dysfunction as a possible basis for obesity. None was found.—*Courtesy, Child Development Abstracts.*

Bronstein, I. P., A. Luhan and Wm. B. Mavrelis.
Sexual precocity associated with hyperplastic abnormality of the tuber cinereum. *Am. J. Dis. Child.* 64: 211. 1942.

Report of a case of a 22-months-old girl exhibiting precocious sexual development, "in whom necropsy revealed what was interpreted as an ectopia of brain tissue between the infundibulum and the mammilary bodies."—*Courtesy, Child Development Abstracts.*

Cantilo Enrique and Carlos Fernandez Speroni.
Endocrinopathies, X. Discussion on two amenorrheas. *Semana méd. 49, II:* 489 (1942).

The first case appeared to be of the asthenic hypoendocrine type but on the basis of well developed genitals with pubic hypertrichosis, a diagnosis of hyperovarian secretion with pituitary inhibition was made. The second patient of pyknic type, showed male distribution of pubic hair and uterine hypoplasia. In this case pituitary overactivity was diagnosed. The first patient had a fasting glucemia of .088 and of .095 after glucose ingestion; the corresponding figures in the second patient were .101 and .285 gm.%. The first patient received 10 mg. progesterone daily, the second 3 injections of estrogen per week (5 mg. each). The treatment was continuous until menstruation occurred. For stabilization of the menstrual cycle, the first patient received treatment with a FSH preparation combined with chorionic gonadotropin during the first part of the cycle. The second patient was treated with estrogen during the predecidual phase. Permanent cure of the amenorrhea was obtained in both cases.—*A.E.M.*

Deming, C. L. and J. T. MacLean.
The incidence of pyelonephritis in successive pregnancies. *J. Urol.* 49: 236. 1943.

This paper is a statistical and critical study of 68 cases of pyelonephritis associated with pregnancy, representing 74 infections, 65 of which occurred during pregnancy and 9 of which developed post partum. Nearly two-thirds of all the cases occurred in the first and second pregnancies. The incidence of infection increases each month, with the maximum occurrence at the fifth and sixth months of pregnancy, which parallels the incidence of occurrence of dilation of the ureter. Both parallel exactly the increased excretion of estrogen and pregnanediol by the placenta during pregnancy. Only 25 per cent of the cases were "cured" at term, yet within 2 weeks of emptying the uterus, 90 per cent were asymptomatic and free of infection.—*H.W.*

Folley, S. J.
"Ghost" formation in subcutaneously implanted tablets of synthetic oestrogens. *Nature* 150: 403. 1942.

Tablets of diethylstilbestrol and hexoestrol implanted in cattle 3 months have the cortex infiltrated with a substance that is chiefly scleroprotein and form an ether-alcohol insoluble membrane that retards absorption of the estrogen from the implant.—*Courtesy Biol. Absts.*

Folley, S. J.
Retarding effect of ghost formation on absorption from subcutaneously implanted tablets of hexoestrol. *Nature* 150: 735. 1942.

Disk-shaped 1-gm. tablets of hexoestrol implanted subcutaneously in cattle maintained a linear absorption curve for the first 10 to 15 days; then the curve continued to fall so long as the experiment lasted. This retardation of absorption is attributed to infiltration of the cortex of the implant by a relatively insoluble protein which forms a "ghost" around the tablet.—*Courtesy Biol. Absts.*

KORBSCH, R.

Treatment of gastric ulcers with progesterone and other cholestenone derivatives. *Deutsche med. Wchnschr.* 68: 417. 1942.

Estrone is known to have a beneficial action on gastric ulcers due to a direct trophic effect on gastrointestinal epithelium and an indirect spasmolytic effect on smooth muscle. Progesterone, in daily injections of 20 mg., is not as effective but does not cause mastodynia or loss of potency in males. A mixture of androstenedione and progesterone, in the same daily dose, is also less active but is useful in treating gastritis. Desoxycorticosterone acetate, 10 to 20 mg., had little effect on ulcers but it is believed that higher doses shold have a marked effect, at least in gastritis.—*Courtesy Biol. Absts.*

NOVAK, E.

The present status of gynecological orgnotherapy. *South. M. J.*, 36: 145. 1943.

This paper is a long review article, comparing the present status of organotherapy in gynecology with that existing 20 years ago. While our knowledge of reproductive endocrinology has been enormously increased during the last 25 years, there has not been a corresponding advance in gynecologic organotherapy. There has been no noteworthy improvement in the treatment of amenorrhea. Organotherapy is frequently of auxiliary value in the treatment of dysmenorrhea and functional bleeding. Progesterone is generally reported to have definite value in the treatment of threatened and habitual abortion. Organotherapy is rational and effective in the treatment of the menopausal vasomotor symptoms, gonorrheal vulvovaginitis of children, and senile vaginitis. The advances made in the knowledge of reproductive endocrinology have facilitated intelligent interpretation of clinical problems and may, each year, add to our therapeutic armamentarium.—*H.W.*

PILCHER, J. D. AND H. TUCHEWICZ.

Premenstrual state in young girls. *Am. J. Dis. Child.* 65: 269. 1943.

The authors studied a 10 year old girl with a persistent vaginal discharge that had been suspected but never proven to be due to gonorrhea. They decided that this discharge was part of the normal premenarchal state, an observation which has been described before only in the German literature (by Soeken). The authors then investigated 49 other girls ranging in age from 8½ to 14 years and concluded that the premenarchal changes: (1) are first noticed between the ages of 8 to 13 years (mean 11 years 4 months); (2) occur usually one month to two years (mean 10 months) before the onset of menses, but may appear suddenly only one week before menarche; (3) are characterized by: a) a white, caseous exudate on the vulva and in the vagina, a swelling and a graying of the hymenal ring, a rugate and pale appearance of the vaginal wall and a normal appearing cervix; b) a change in the reaction of the vaginal secretion from alkaline to acid; and c) a change in the type of flora from cocci to bacillary (although acid-forming enterococci are occasionally found with or without the bacillary group); (4) usually but not always precede other signs of puberty such as development of the breasts and growth of the vulvar hair; (5) persist after menstruation; (6) are similar to the changes induced by estrogen therapy; (7) are probably responsible for the spontaneous cure of gonorrheal infection; and (8) are often mistakenly diagnosed as gonorrheal vaginitis.—*E.C.R.,Jr.*

PREISSECKER, E.

Studies on the tolerance of stilbene. *Deutsche med. Wchenschr.* 68: 428. 1942.

Choline increases tolerance of women to diethylstilbestrol and its dipropionate. Side effects are less frequent with a double compound of diethylstilbestrol and choline than with diethylstilbestrol alone. Studies with other esters of stilbestrol are reviewed.—*Courtesy Biol. Absts.*

SCHITTENHELM, A.

A critique of hormone therapy. *Deutsche med. Wchnschr.* 68: 33. 1942.

Modern applications are reviewed for pituitary, thyroid, adrenal cortex and sex hormones, as well as for insulin and diethylstilbestrol. In the introduction, a warning is given of the inapplicability to diagnosis of the interferometric method of the Abderhalden reaction.—*Courtesy Biol. Absts.*

SCHNEEBERG, N. G., W. B. LIKOFF, AND I. E. RUBIN.
The pituitrin concentration test of renal function. *J. Lab. & Clin. Med.*, 28: 757. 1943.

In a series of 100 unselected hospital cases, 4 procedures for testing renal function were compared: the Fishberg test; the Volhard dilution test; the Volhard dilution test plus 0.5 cc. surgical pituitrin; and the pituitrin concentration test of Sodeman and Englehardt. All procedures were performed in 25 patients, and the Fishberg and pituitrin concentration tests in the remaining 75. There was a 90 per cent correlation in the results obtained by the Fishberg technic and the pituitrin concentration test. In 4 cases the pituitrin test failed entirely, and in 6 it apparently reflected the condition of the kidney more accurately than did the Fishberg procedure. When the specific gravities of the urines ranged between 1.015 and 1.025, statistical analysis of the results showed the possibility of considerable disagreement between the 2 tests. The authors believe many more cases must be studied before the relatively simple pituitrin test can be used in place of the Volhard or Fishberg procedures in the true evaluation of kidney function.—*T.H.McG.*

SEXTON, D. L.
Emaciation and endocrine dysfunction. *South M. J.* 36: 276. 1943.

Eight cases are presented of patients whose chief findings were emaciation, weakness, and anterior pituitary failure, the thyroid, adrenals and gonads being markedly affected. In 6 of the 8 patients, history of a definite psychological disturbance was elicited, while in the other 2 the onset was insidious. From the experimental and clinical evidence available, functional pituitary failure may follow inanition. The clinical signs are not unlike those seen in early Simmond's disease, with anatomical destruction of the anterior hypophysis. The author believes there is an inherent weakness in the pituitary gland that is functionally depressed by inanition, producing gastric disturbances and anorexia as does Simmond's disease. He recommends correction of the psychic upset, and support of adrenal deficiency, with substitutional hormone therapy added as needed.—*H.W.*

SHUTE, EVAN
Influence of estrogens on genuine pre-eclampsia and eclampsia. *Am. J. Surg.* 59: 478. 1943.

Presented in detail are case reports of three convulsive eclamptics and of eight true pre-eclamptics. One of the latter was induced and all remained ambulatory. All cases were favorably influenced by administration of estrogens, including estradiol benzoate and diethylstilbestrol. This therapy is more effective in the prophylaxis than in the control of convulsive eclampsia as could be anticipated. Author believes that blood estrogen assays are essential to recognition of a true pre-eclamptic state since administration of estrogens to unproven pre-eclamptics do no good and may do some harm.—*D.A.M.*

SHUTE, EVAN
Vitamin E in the prophylaxis of abruptio placentae. *Surg., Gynec. and Obstet.* 75: 515. 1942.

Case reports are presented to show that: abruptio placentae can be foreseen during pregnancy by means of a blood estrogen assay; the signs disappear promptly if vitamin E is administered at once; "the vitamin E used must be a potent preparation. The dose usually rises as pregnancy proceeds and must always be the dose required to control symptoms if any particular woman's pregnancy. . . . It must be given until delivery."—*Author's Abstract.*

SHUTE, EVAN.
Vitamin E in habitual abortion and habitual miscarriage. *J. Obst. and Gynec. Brit. Emp.* 49: 534. 1942.

Brief details are presented of all the pregnancies, both before and during treatment with vitamin E or other agents, of 17 women with histories of true habitual abortion and 5 with habitual miscarriage. No evidence was found that vitamin E, even when given in large doses, was of any value in the treatment of habitual abortion. There was some evidence that vitamin E therapy might be of some value in the treatment of habitual miscarriage.—*Author's Abstract.*

TALBOT, N. B., A. M. BUTLER, R. A. BERMAN, P. M. RODRIGUEZ AND E. A. MACLACHLAN.
Excretion of 17-ketosteroids by normal and by abnormal children. *Am. J. Dis. Child.* 65: 364. 1943.

A series of measurements of the urinary excretion of 17-ketosteroids has been made on normal subjects ranging in age from a few hours to over 47 years. Of these, 31 were made on 31 girls ranging in age from 4 to 18 years; 69 were made on 69 boys ranging in age from a few hours to 18

years. The output is low from birth to approximately 10 years, and then gradually rises as the subjects approach 18 years. Boys did not excrete significantly greater amounts of these substances than girls suggesting that the adrenal cortex is the chief site of origin of the 17-ketosteroids during childhood. The rise in the output after 10 years implies a relation between the secretory activity of the adrenal cortex and growth and development. From the normal range it is possible to tell whether a given value is abnormally high at any age, but since values approximating 0 may be considered normal for children under 10 years, detection of abnormally low excretion under that age is not possible. Children of 12 years should excrete at least 1 mg. of 17-ketosteroids daily; of 18 years approximately 9 mg. daily. Day to day variation in the excretion by a single subject was investigated. An analysis of 80 assays on 2 normally menstruating (adult) women showed that two-thirds of the values fell within ± 15 and ± 12 per cent of the average value for each subject, respectively. In no instance did any value obtained for one subject deviate from her average value by more than ± 30 per cent. Approximately similar results were obtained in the assays of a normal man and of two children. A tendency toward a moderate elevation in output of 17-ketosteroids was observed in 5 apparently "normal" children with physiologic sexual precocity and in 7 abnormally overweight children. These latter also were found to have accelerated development and growth, suggesting that excessive obesity may favor a hyperexcretion of 17-ketosteroids. Abnormally low excretion was found in children over 12 years whose growth and development were retarded, including 9 patients with presumable deficiency of the anterior lobe of the pituitary gland and 12 patients with hypothyroidism who were receiving thyroid therapy. This suggests either that more thyroid medication is required for the excretion of a normal amount of 17-ketosteroids than for an "adequate" clinical response, or that "hypothyroidism" is not necessarily a simple disease, which is characterized only by a lack of thyroid hormone. The excretion of 17-ketosteroids by 13 patients with mongolism was not consistently abnormal. In adults, 89 determinations were made on 4 normal women, and 12 on 3 normal men. The women had values which corresponded closely to those obtained for children 17 to 18 years old (average 7 mg.). Men excreted more (average 11 mg.) than women or older children. —*E.C.R., Jr.*

VAN WAGENEN, G., AND R. H. JENKINS
Pyelo-ureteral dilatation in successive pregnancies. *J. Urol.* 49: 228. 1943.

The demonstrable dilatation of the ureter which occurs in approximately 80 per cent of all pregnant women has been termed "physiological hydroureter of pregnancy." Stasis caused by this facilitates bacterial invasion and eventual pyelitis. The writers have previously shown that ureteral dilatation also occurs in the later months of pregnancy in the rhesus monkey, and persists after surgical removal of the fetus, in one case making its appearance three months after the fetus had been removed. In the present paper the urinary tracts of 10 monkeys (macaca mulatta) have been visualized by excretory urography through 37 normal pregnancies. Dilatation is at a maximum in the first pregnancy, and decreases with succeeding pregnancies. If such conditions exist in the human, infection should be less frequent after the first pregnancy. The hypothesis of a placental-endocrine cause of this dilatation was tested by the use of stilbestrol, theelin and progesterone. It was impossible, with the estrogens, in the amount used, to reduce existing dilatation in late pregnancy or to speed up post-parturitional regression; nor was premature dilatation induced with progesterone.—*H.W.*

WATSON, B. A., N. YOLTON, AND L. RAULS.
Sex hormone assays in the menopause: their clinical significance. *J. Lab. & Clin. Med.*, 28: 732. 1943.

Data and conclusions were drawn from the analysis of from 2 to 4 complete 24-hour specimens of urine from each of 28 women with well-known signs and symptoms of the climacterium. Of these women, 12 had had an artificial menopause. Estrogens were calculated by the ovariectomized-mouse method and reported in gammas of estrone; 17-ketosteroids were estimated by a modification of the Zimmerman method and reported as milligrams of androsterone. The average mean estrone for all cases was about 6.8; for the menopausal group with "flashes," 5.61; and for about those without "flashes," 7.68; the range of values was very wide (1.1 to 22.9). Mean androsterone values were not significantly altered, although individual variations were marked. The cases could be grouped into 3 categories as a result of the hormone determinations: Those with (a) a lack of female sex hormone; (b) a deficiency of male sex hormone; and (c) a sex hormone imbalance with individual values in normal limits,

e.g., low normal male and high normal female, or vice versa. In each instance, therapy was directed with reportedly good results toward replacement of the hormone found to be diminished in the urine. The authors conclude that a satisfactory correlation can be made between the titer of sex hormones of the urine and the clinical results to be expected in treating women with climacteric symptoms.—*T.H.McG.*

WETZEL, N. C.
Assessing the physical condition of children. III. The components of physical status and physical progress and their evaluation. *J. Ped.* 22: 329. 1943.

The author employs a series of photographs of the same group of children to illustrate the basic meanings that can be attached to physique, development, nutritional grade, and age, separately, and to show how these may be reassembled by means of a "grid" (which he has devised) for the assessment of the physical condition of these children. He emphasizes the ease with which a group can be "screened" by this technique to isolate the individuals who need extensive investigation because of their unfavorable physical state.—*E.C.R.,Jr.*

GONADS

BERGMAN, R. T.
Carcinoma of the prostate: Recent advances in its treatment. *California & West. Med.* 58: 71. 1943.

Hormonal treatment relieved pain in nearly 90% of the author's cases; caused an improvement in appetite, gain in weight, and an actual regression in size of the gland after several months' treatment.—*Author's Abstract.*

BROWN, E.
Treatment of gonorrheal vulvovaginitis with estrogens. *Am. J. Dis. Child.* 64: 211. 1942.

Thirteen cases of gonococcic and 6 of nonspecific vaginitis in prepubertal girls treated successfully with estrogens are reported.—*Author's Abstract.*

GOLD, S.
Estrogen therapy in testicular hypofunction. *Canad. M. A. J.* 48: 231. 1943.

Two male patients with diminished sexual potency were treated with estrogenic hormone following a course of testosterone propionate. A third patient received alternate injections of androgenic and estrogenic hormones. The estrogenic hormones were thought to increase libido and potency; there was no antagonism between the male and female hormones used, in the given quantitites and proportions. There was no beneficial effect on spermatogenesis in the patients with total aspermia. The efficacy of the drug was not maintained over a period of time.—*P.H.S.*

JONES, G., E. SEEGAR, G. O. GEY, AND M. K. GEY.
Hormone production by placental cells maintained in continuous culture. *Bull. Johns Hopkins Hosp.* 62: 26. 1943.

Pure strains of cells from human placental tissue were maintained in continuous culture and assays for cyonin (chorionic gonadotropin) and estrogen made on the supernatant cell free culture medium. Cyonin was demonstrated as indicated by the presence of corpora lutea in the 21-day old rat ovary; estrogen was not present in increased amount over the control tissue culture medium. —*P.H.S.*

LAPIN, J. H., W. KLEIN, AND A. GOLDMAN.
Cryptorchidism, *J. Ped.* 22: 175. 1943.

The authors treated 200 boys for cryptorchidism in their endocrine clinic during the past nine years but are able to report on only 39 boys who were followed for from two to nine years. Successful descent into the scrotum was obtained in only six instances (15.3 per cent). The following conclusions were reached: Treatment of cryptorchid testes is advisable to relieve the deficiency of androgenic hormone formation, spermatogenetic activity and the psychological handicap, provided a procedure is adopted to minimize the dangers of pubertas praecox, of osseous retardation and of testicular atrophy. The optimal age for treatment is 14 years. A preliminary test of endocrine therapy is fully justified in any cryptorchid testes not clearly ectopic. Chorionic gonadotropic hormones are only ones free from theoretical objections. The maximal dosage should be given in small frequent amounts over a six-week period without any rest period. If the cryptorchid testes do not descend following this dosage and for this period, operation should be immediate and further hormone can be given after the testes is embedded in the scrotum. Ectopic testes should benefit from a simular pre- and post-operative procedure except where complicated by a substantial inguinal hernia.—*M.B.G.*

RUPEL, E.
Prostatic cancer; an evaluation of treatment by castration. *South. M. J.* 36: 251. 1943.

The results of treatment of 26 patients with prostatic cancer by testicular excision, and 8 by stilbestrol treatment. There were three deaths, two patients who regressed after immediate improvement had to be placed on stilbestrol, while all but one of the patients obtained immediate relief from pain after castration. Stilbestrol had a delayed action. A review of the rationale of this treatment is given.—*H.W.*

THOMPSON, W. O.
Endocrine problems in the male. *Nebraska M. J.* 28: 9. 1943.

Discussing treatment of undescended testes, author says material of choice is chorionic gonadotropin because in most instances, the testes can respond to stimulation. The only exceptions are those cases in which both testes are within the abdominal cavity. It is preferable that treatment be carried out at an early age. When necessary, operative procedures are made easier by pre-treatment with chorionic gonadotropin.—*D.A.M.*

WARREN, S., AND K. W. OLDHAUSEN.
Interstitial cell growths of the testicle. *Am. J. Path.* 19: 307. 1943.

Two cases of hyperplasia and 2 cases of tumors of the interstitial cells of the testis are reported There is included a detailed survey of the literature on interstitial cells of the testis covering the following topics: in the normal testis, relationship to hormonal influences and hyperplasia of in relation to spermatogenesis. Criteria for classifying either as local tumor or as hyperplasia are presented. Hyperplasia occurs principally at or above 45 years of age in atropic testicles and is discovered chiefly at autopsy. Local tumors occur predominantly at or below 45 years of age in testicles larger than normal and are generally discovered during life and removed surgically. If the testicle contains an increased number of interstitial cells, especially if the seminiferous tubules are partially or completely destroyed the patient should be carefully followed for more than ten years for the appearance of metastases as indication of malignancy.—*M.L.M.*

WELLS, H. GIDEON.
Seminoma developing in an undeveloped genital anlage. *Arch. Path.* 35: 590. 1943.

A case is reported of complete failure of the right genital anlage to develop, associated with immaturity of the left genital anlage. At the age of 47 the patient died with a retroperitoneal seminoma, apparently arising in the rest of undeveloped right genital anlage.—*Author's summary.*

ZONDEK, B.
The importance of increased production and excretion of gonadotropic hormone for diagnosis of hydatidiform mole. *J. Obst. & Gynaec. Brit. Emp.* 49: 397. 1942.

Increased excretion of prolan A (FSH), while inadequate for diagnosis of pregnancy in itself, is of value in the diagnosis of hydatidiform mole. A titration value of over 500,000 MU of prolan A and 200,000 MU of prolan B (LH) per liter urine is strongly indicative of mole. Urine analyses should be supplemented by serum assay. In positive cases the latter contains quantities of both A and B, higher than that found in urine. Spinal fluid, moreover, which normally is negative for B, becomes positive in hydatidiform mole and in general the higher the titer the more certain the diagnosis. Demonstration of the prolans in tissues is also of diagnostic importance; a placental tissue titer of over 800 MU per gm. makes diagnosis of malignant degeneration probable, and such diagnosis is certain when values rise to more than 200,000 MU, particularly if the value of A is so elevated. Following pregnancy, persistence of prolan excretion more than one week post partum is indicative of mole or of luteal cyst. Three cases are presented illustrative of the above generalizations.—*H.O.H.*

HYPOPHYSIS

ANDERSON, A. AND WM. R. MURLIN.
Antagonism of pitressin and adrenal cortical extract in human diabetes insipidus. *J. Pediat.* 21: 326. 1942.

The physiologic antagonistic action of adrenal cortical extract and pitressin on the excretion of sodium, chloride, and water has been confirmed in the human subject with diabetes insipidus. Adrenal cortical extract is unable to produce an increased excretion of potassium unless pitressin is supplied. The suggestion is offered that facultative reabsorption of water as induced by pitressin must be in progress before the kidney tubule can selectively excrete sodium and potassium ions.—*Author's Abstract.*

GREENE, B. A.
Posterior pituitary extract in anesthesiology. *Ann. Surg.* 116: 898. 1942.

Author advocates more frequent use of posterior pituitary extracts in operating rooms than has been customary in the past. By their judicious use, the surgeon can secure a more stable peripheral circulatory system, a more relaxed abdominal field, better hydration, less blood loss, more expeditious and less traumatic surgery and a decreased likelihood of postoperative intestinal atony.—*D.A.M.*

LURIE, L. A. AND S. LEVY.
Lawrence-Moon-Biedl syndrome. A report of two cases with unusual combinations of heredofamilial deviations. *J. Ped.* 21: 793. 1942.

Both patients presented a combination of obesity, genital dystrophy, dwarfism, mental retardation, syndactylism, familial occurrence and nerve deafness. One patient in addition presented the symptom of tapitoretinal degeneration. Electroencephelogram showed abnormalities consistent with a rather severe cerebral dysrhythmia. Electrocardiographic tracings revealed normal findings, thus excluding the possibility of congenital heart disease. No skull deformities or skeletal defects were found on roentgenograms. The chemical constituents of the blood were within normal limits.—*M.B.G.*

SHEEHAN, H. L., AND M. G. B. MCLETCHIE.
Simmond's disease due to postpartum necrosis of the anterior pituitary. *J. Obst. & Gynaec. Brit. Emp.* 50: 27. 1943.

The literature is reviewed and a case is reported of Simmond's disease which arose from postpartum necrosis of the anterior pituitary. It followed a typical clinical course, and the patient remained well nourished. Death occurred 6 years after delivery. Autopsy findings are included. Such cases, as verified by autopsy, now number 48.—*H.O.H.*

WAGNER, R.
Galactose tolerance test in endocrine disorders in children. *Am. J. Dis. Child.* 65: 207. 1943.

The author applied the galactose tolerance test of Althausen, Lockhart, and Soley to 49 children suspected of having reduced pituitary function. These subjects were diagnosed under the headings: hypogonadism, obesity (with the three subdivisions exogenic, constitutional and "Frohlich-like"), cryptorchidism (with or without endocrine features), transitory infantilism, amenorrhea and irregularities of menstruation, acne occurring during puberty, alopecia areata, gigantism, pituitary dwarfism and hepatomegaly of unknown cause. A flat curve was anticipated in these patients because they were assumed to have reduced thyroid function due to decreased output of pituitary thyrotropic factor. The basal metabolic rate was below minus 15 in 11 of the cases. Most of the 49 children showed flat dextrose tolerance curves. The results of the galactose tests were analyzed in terms of the surface area bounded by the plotted curve. Abnormally flat galactose tolerance curves were obtained only for patients with hypogonadism and abnormally high curves only for pituitary dwarfs. The author concluded that the galactose tolerance test was of more value for this series of patients than the dextrose tolerance test. He also determined the rise induced by the galactose in the dextrose content of the blood. The dextrose level was hypoglycemic only in subjects with high galactose tolerance curves. No normal standards for the galactose tolerance test in children were determined; the analysis of the data was based on the standards for adults obtained by Althausen and co-workers.—*E.C.R., Jr.*

PANCREAS

FISCHER, E., S. MACKLER AND H. MARKS.
Long term growth of diabetic children. *Am. J. Dis. Child.* 64: 413. 1942.

The growth characteristics of a group of 44 diabetic children from low income families, studied over a period of 5 to 10 years or longer, are reported. Of the 42 children whose height at approximately the time of onset of diabetes was known, all but 6 were either average or tall for their age when the disease began. The average rate of growth in height of both boys and girls was below that generally expected in normal children.—*Courtesy, Child Development Abstracts.*

JACOB, W.
On the advancement of therapy of diabetes based on clinical and followup results in the last decade. *Deutsche med. Wchnschr.* 68: 419. 1942.

Experience with 1266 diabetics, of whom 57% were ♂, is summarized from 1930 to 1940. Age incidence is noted. Mortality was 6.5% for ♂♂, at an average age of 61 years, and 6.6% for ♀♀, at an average age of 58 years. Fourteen died in coma, and the remainder from various intercurrent diseases or degenerations. Difficulties were

encountered in ⅓ of the patients in following an insulin regime, and the use of various nostrums is noted. Cirrhosis of the liver occurred in 2 patients taking quanidine derivatives. In practice, therapy of diabetes is far from ideal.—*Courtesy Biol. Absts.*

KIRSHBAUM, J. D., AND N. SHURE.
Alcoholic cirrhosis of the liver: a clinical and pathologic study of 156 fatal cases selected from 12,267 necropsies. *J. Lab. & Clin. Med.* 28: 721. 1943.

This is a very detailed analysis of 356 cases of alcoholic cirrhosis occurring in 12,267 consecutive autopsies. The report includes data related to age, racial and sex incidence; alcoholic history; the appearance of jaundice and ascites; esophageal varices; variations in blood pressure; the weights of the liver and spleen; pectoral alopecia; the co-presence of carcinoma of the liver; and pancreatic changes. Of endocrine interest are the pancreatic changes. Striking variations in weight of the pancreas were confined to isolated cases, 1 weighing as little as 30 gm., and another as much as 230 gm. In 36.2 per cent, fibrosis of the pancreas was well marked. Five patients had pancreatic calculi. Parenthetically the authors comment that cirrhosis has been found in 50 per cent of all of their autopsied cases of pancreaticolithiasis.—*T.H.McG.*

O'BRIEN, C. S. AND J. H. ALLEN.
Ocular changes in young diabetic patients. *J. A. M. A.* 120: 190. 1942.

Retinopathy was found to occur in 4 per cent of the more than 500 diabetic patients who were the subjects of this study. The authors attribute this disorder to the diabetes "since it has the same appearance of that occurring in older patients and it is seen in those in whom no other diesease can be found." Diabetic cataract was found in almost 14 per cent of 260 patients under 21 years of age.—*Courtesy, Child Development Abstracts.*

PARATHYROID

BRAKELEY, E.
Late rickets. *Am. J. Dis. Child.* 65: 314. 1943.

A girl is described who at the age of 11 had typical rickets by X-ray. The serum calcium was 11.2 to 12.5 mg. per cent, the serum phosphorus 3.29 to 3.59 mg. per cent, and the serum phosphatase 29 Bodansky units. Healing was induced after three months by the relatively large dose of 40,000 U.S.P. units of vitamin D. Eighteen months later x-rays showed decalcification of the shafts of the bones; and during the next year the serum calcium level rose gradually to 15.0 mg., the phosphorus level became low (1.5 to 3.0 mg.), and the serum phosphatase level at first rose to 39 and then fell to 16.8 Bodansky units. These changes were considered to be due to secondary hyperparathyroidism. An exploratory operation was performed, but the parathyroid glands were not identified. The patient then received 800 r of x-radiation to each side of her neck, after which her blood values changed to calcium 12.5 mg., phosphorus 4.2 mg., and phosphatase 12.5 Bodansky units. Six months later the serum calcium was again elevated (15.0) and the serum phosphorus decreased (3.1), while the serum phosphatase had dropped to nearly normal (10.0). X-radiation to both sides of the neck in the same dosage was repeated. Four months later, the calcium was 8.5, the phosphorus 2.23, and the phosphatase 6.7. Clinically the patient was improved; she had grown 1¾ inches, gained 6 lb., and begun menses (age 15). In 18 months since the x-radiation, the serum values have remained normal, the last figures being calcium 10.5, phosphorus 3.7, and phosphatase 6.0. X-rays of the long bones showed recalcification. The author points out that it is impossible to prove whether these alterations were a result of the irradiation or would have occurred without further treatment.—*E.C.R., Jr.*

SPIRA, LEO.
Fluorosis and the parathyroid glands. *J. Hyg.* 42: 500. 1942.

There is a close similarity between the dental changes produced experimentally in the rat by parathyroidectomy and mottled teeth as seen in man and known to be caused by protracted ingestion of toxic amounts of fluorine. In view of the fact that both parathyroidectomy and fluorine produce dystrophies in tissues regulated by the parathyroid glands it is concluded that, in man, mottled teeth, certain dermatoses, mottled nails and alopecia may be due to a disturbance of these glands brought about by the ingestion of toxic amounts of fluorine in drinking water.—*Author's Abstract.*

THYROID

BARATZ, J. J. AND H. BEHRENDT.
The heart in children with thyroid deficiency. *Am. J. Dis. Child.* 64: 471. 1942.

The results of cardiac examinations (roent-

genograms and electrocardiographic recordings) of 3 children with thyroid deficiency; and follow-up notes on a patient with myxedema heart, originally examined in 1936, are reported. In none of the 3 more recent patients was the cardiac enlargement as pronounced as in the original patient, but the electrocardiographic changes at the beginning of observation and during treatment were similar in all 4 cases. The pathogenesis of cardiac enlargement associated with cretinism is discussed.—*Author's Abstract.*

CASAUBON, ALFREDO, CARLOS I. GARCÍA DÍAZ AND ANÍBAL LETAMENDI.
Graves' disease in childhood. *Semana méd.* 50: 210. 1943.

Graves' disease in three girls of preadolescent age is described. The treatment consisted in rest, iodine medication and radiotherapy. Cure including regression of the exophthalmos was obtained.—*A.E.M.*

HEREDIA, PABLO.
Angina pectoris of thyroidal origin. *Semana méd.* 50: 357. 1943.

Among the four possible relationships between angina and thyroid affection only one type is recognized as caused by thyroid disease, namely angina of myxedema with improvement or cure produced by thyroid treatment. Four cases are reported to illustrate this assertion.—*A.E.M.*

HILL, A. M. AND J. E. WEBBER.
Serum phosphatase values in children showing retardation in osseous development and low metabolic rates. *J. Ped.* 22: 325. 1943.

This study confirms Talbot's observation that the serum phosphatase tends to be below normal in children with hypothyroidism. The authors investigated 23 children who exhibited symptoms of mild hypometabolism and who, in addition, showed either marked osseous retardation or low metabolic rates, and found that 20 of them had serum phosphatase values of 5.6 Bodansky units or less. The normal values in children are: Bodansky —7.5 units (average), 5 to 14 units (range); Talbot—7.2 units (average), 4.5 to 12 units (range); authors—5 to 9.7 units (range, based on 14 children). Thyroid therapy caused low serum phosphatase levels to approach the normal range.—*E.C.R.,Jr.*

MAY, W.
Treatment of hyperthyroidism with fluorotyrosine. *Deutsche med. Wchnschr.* 68: 104. 1942.

Fluorotyrosine is recommended for hyperthyroidism. Studies are cited on the relation of clinical signs of hyperthyroidism to glycogenolysis; the inhibiting effect of NaF on hepatic glycogenolysis; the partial antagonism between F and I; and treatment of Basedow's disease with fluorotyrosine. Over 3000 hyperthyroid patients have been treated with fluorides. Fluorotyrosine represents a safe agent for treatment of difficult cases as well as for the increasing number of cases of hyperthyroidism due to nervous strain and exhaustion in war. Five case reports are given, in which fluorotyrosine substitutes for iodine in Basedow's disease. The effects of this agent are beyond those of rest, diet and climate. —*Courtesy Biol. Absts.*

VELHAGEN, K.
Exophthalmos in the light of recent advances. *Deutsche med. Wchnschr.* 68: 81. 1942.

The condition of the orbit is maintained through a complex interaction of autonomic impulses and hormonal influences, part of the latter directly from the anterior pituitary and part indirectly from different glands and sites elaborating the antithyreotrophic or antiexophthalmos hormone. Exophthalmos results from disturbance of this equilibrium. Direct autonomic effects on the orbital muscles are of less importance than those received by the endocrine glands.—*Courtesy Biol. Absts.*